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Original Communications

CARCINOMA OF THE UTERINE CERVIX*

Interval Report on Treatment, Results, and Complications

GEORGE VAN S. SMITH, M.D., AND RICHARD DRESSER, M.D., BROOKLINE, MASS.
(From the Free Hospital for Women)

THE last paper on carcinoma of the uterine cervix from this hospital covered 780 consecutive, previously untreated, pathologically confirmable cases from Oct. 1, 1902, through 1933.[1] Only those with clearly invasive cancer were included. Our patients with "carcinoma in situ" are treated and followed as a separate group. The present report will summarize the above series, to which have been added three cases as a result of re-evaluating their pathologic sections, bringing the results up to date, and will include a new five-year series of 328 similar cases from Jan. 1, 1934, through Dec. 31, 1938, thus encompassing a total of 1,111 cases. The pathologic sections of this new series have also been carefully rechecked. Acknowledgment is made to the other members of the staff of the Free Hospital for Women for the inclusion of their cases and help in gathering data. Actually, this is a report from the staff. Therapeutic x-radiation was given by Dr. John W. Meachen until the fall of 1937 and since then by one of us (R. D.). For the use of the supervoltage (1,000 kv.) apparatus, we are grateful to the administrators of the Collis P. Huntington Memorial Hospital, now a unit of the Massachusetts General Hospital.

Review of Cases

To facilitate presentation and the comparison and evaluation of results, the whole series is divided into groups according to convenient intervals of time and in relation to changes in treatment. "Hysterectomy" in the tables covers the complete and Wertheim procedures and abdominal excisions of the cervical stump. The postoperative deaths listed in the tables were due to shock, peritonitis, pneumonia or embolism following surgery, and, most often, to sepsis after radium. Embolism and agranulocytosis each accounted for a death after application of radium.

*Presented before the Obstetrical Society of Boston, Nov. 21, 1944.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

1902 to 1913 (Table I)

One of the patients, alive at 5 years after treatment, died of cancer of the stomach (clinical diagnosis) 15 months later. Her cervical cancer had been an early one. Another died of diabetes. The 6 patients alive at 10 years were alive at 20 years; 2 were dead of cardiovascular disease at 25 years; the remaining 4, 5 per cent of the whole group, were alive at 29 to 32 years. One of the latter had had metastatic cancer at the bifurcation of the left common iliac vessels and had been operated upon by the late Dr. William P. Graves. There was one complication in this group, a vesicovaginal fistula from radium given for a recurrence. Our purpose in following the survivors longer than really necessary is to obtain information concerning longevity in cured patients and the incidence of new primary malignancies.

TABLE I. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, OCT. 1, 1902, TO 1913, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 10 YEARS	ALIVE AT 10 YEARS
Untreated	8		2	0			
Cauterization	37	3	4	0			
Amputation of cervix	6	0	1	2	0	1	1
Hysterectomy	32	5 (16%)	1	8 (25%)	2	1	5 (16%)
Totals	83	8 (11%)	8 (10%)	10 (12%)	2	2	6 (7%)

TABLE II. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1914 TO 1918, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 10 YEARS	UNTRACEABLE AT 10 YEARS	ALIVE AT 10 YEARS
Untreated	9		2	0				
Hysterectomy	26	3 (12%)	0	11	3	0	1	7
Hysterectomy; radium	11	0	0	2	0	0	0	2
Radium; hysterectomy	10	1 (10%)	1	2	1	1	0	0
Radium	23	0	0	0				
Totals	79	4 (6%)	3 (4%)	15 (19%)	4	1	1	9 (11%)

1914 to 1918 (Table II)

Radium was first used in this hospital late in 1916. The technique of application and dosage employed during earlier years, having been described[1] and now obsolete, will not be given here. Pneumonia caused the death of one patient who was well at the fifth year after treatment. Of the 9 patients alive 10 years after therapy, one died of recurrence 5 months later and one died of presumed recurrence at 14 years and 6 months. Seven, 9 per cent of the group, were alive at 15 years; 2 were dead of cardiovascular disease at 20 years; 2 more were dead of cardiovascular disease at 25 years; the remaining 3, 4 per cent, were well at 27 to 29 years. Complications from treatment occurred in 5 patients: one incisional hernia, one vesicovaginal fistula of surgical origin and one from radium, 2 patients developed both vesicovaginal and rectovaginal fistulas from radium.

1919 to 1923 (Table III)

Of the 14 patients alive at 10 years after therapy, one died 2 months later of recurrence and 3 died of cardiovascular disease before the fifteenth year, leaving 10, 8 per cent, fifteen-year survivors. One became untraceable and one died of sepsis at 18 years and one died of cancer of the stomach (clinical diagnosis) at 19 years and 7 months, leaving 7, 6 per cent, alive at 20 years. Complications: One incisional hernia; two deaths from intestinal obstruction, 14 months and 6 years, respectively, after surgery; and one rectal obstruction from radium given for biopsied recurrence—colostomy was performed, the patient died of cardiovascular disease in her ninth postradium year.

TABLE III. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1919 TO 1923, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	UNTRACEABLE AT 10 YEARS	ALIVE AT 10 YEARS
Untreated	5		1	0			
Hysterectomy	18	1 (6%)	0	9	5	1	3
Hysterectomy; radium	13	0	0	5	2	0	2
Radium; hysterectomy	2	0	0	0			
Radium	81	1	1	13 (16%)	3	0	9 (11%)
Totals	119	2 (2%)	2 (2%)	27 (23%)	10	1	14 (12%)

TABLE IV. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1924 TO 1928, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	DIED OF INTERCURRENT DISEASE BEFORE 5 YEARS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 10 YEARS	UNTRACEABLE AT 10 YEARS	ALIVE AT 10 YEARS
Untreated	7			0	0				
Amputation of cervix; radium	1	0	1	0	0				
Hysterectomy	24	1 (4%)	1	0	15	1	2	1	11
Hysterectomy; radium	8	0	0	0	2				2
Radium	186	2 (1%)	6	5	47 (25%)	8	3	1	35 (15%)
Totals	226	3 (1%)	8 (4%)	5 (2%)	64 (28%)	9	5 (2%)	2	48 (21%)

1924 to 1928 (Table IV)

The improved results for this period are attributed to the giving of single doses of 200 or 225 mg. of radium, screened with 0.5 mm. of silver and 0.5 or 1.0 mm. of brass, for 24 to 30 hours, 6,000 mg. hr. being the maximum dose, the brass screening being supplied by the tubes and "pillboxes" used in applying the silver capsules containing the 25.0 or 50.0 mg. of radium.

One patient in this group had primary *carcinoma of the breast* at the time her cervical cancer was treated. The 8 deaths from intercurrent disease before the fifth year after treatment were due to cardiovascular conditions. The 5 deaths from intercurrent disease between the fifth and tenth years were due to the following: cardiovascular disease, 2; pneumonia, 1; peritonitis following operation for primary *carcinoma of the sigmoid,* 1; and primary *carcinoma of the rectum,* 1, this last cancer developing in an area that had been exposed to radium.

Of the 48 patients alive at 10 years, one died of recurrence 15 months later; 5, who were well at 12 to 13 years, became untraceable; and 7 died of intercurrent disease as follows: cardiovascular, 4; pyelonephritis from renal calculi, 1; primary *carcinoma of the vulva,* 1; and *melanoma* of choroid of eye, 1. Thirty-five patients, 15 per cent, were known to be alive at 15 years.

Two patients had complications from surgery, an incisional hernia and a vesicovaginal fistula; and 6 from radium, an obstruction of the rectosigmoid (colostomy, later restoration of intestinal continuity, well at 16 years after radium), a proctitis resulting in stricture, a rectovaginal fistula, a cystitis, a vesicovaginal fistula and a stricture of the ureter resulting in left nephrectomy at 15 years and 2 months.

Fifty-nine, 26 per cent, of the 226 patients in this group had cancers classified as limited to the cervix. Thirty-eight, 64 per cent of them, were alive at the fifth year and comprised 59 per cent of the 64 five-year survivors. The 26, 44 per cent, alive at 10 years comprised 54 per cent of the 48 ten-year survivors. Similarly, the 20, 34 per cent, alive at 15 years comprised 57 per cent of the 35 fifteen-year survivors. Thus, less than 60 per cent of the good results during this period were achieved in patients with a good prognosis based on clinical examination.

1929 to 1933 (Table V)

During this period three changes in treatment were introduced. The first was initiated in the fall of 1930 and consisted of administering radium in 2 doses of 2,000 to 3,600 mg. hr. each, within 10 to 21 days of each other, for a total of 4,800 to 6,000 mg. hr. Early in 1931 the second change was made. Radium applicators of 1.0 mm. brass with additional screening of 1.0 mm. lead were much more frequently employed. Then, in the spring of 1931, x-ray therapy was begun by Dr. John W. Meachen, who used a standard 200-kv. apparatus of that time. His usual procedure was to give four treatments totaling 1,600 r. immediately after the first application of radium and to repeat this in about two months. A third series was quite often administered six to twelve months later and during this interval even a fourth series was sometimes added. Actually, during the years 1931 to 1933, there was a considerable amount of exploratory variation in x-ray therapy as previously described.[1] A gratifying improvement in results ensued in spite of a distressing number of deaths and complications attributable to treatment and an increase of deaths from intercurrent disease.

Three of the deaths from intercurrent disease before the fifth year were from pneumonia, four were of cardiovascular origin, and one resulted from mastoiditis. Between the fifth and tenth years after treatment, 13 patients died of cardiovascular disease and one of suicide.

Deaths From Irradiation.—In the last paper[1] three deaths in this group were attributed to irradiation. Seven deaths are now ascribed to irradiation; four before the third year after treatment, two between the fifth and tenth years, and one at 13 years and 10 months. Irradiation, we feel sure, caused or hastened other deaths but we have not blamed treatment unless the evidence was convincing. Four of the patients dying as a result of irradiation complications had had cancers apparently limited to the cervix. (1) Mrs. M. D. (22,778) died of chronic pelvic sepsis associated with fecal drainage from the cervix one year after the start of treatment. (2) Mrs. J. McK. (21,324) died thirteen months later from the results of ureteral and bowel injury which followed overtreatment, viz., 8,300 mg. hr. and 7,440 r. given over a period of six months. (3) Mrs. E. C. (22,075) died twenty months after first treatment of pyelonephritis from ureteral injury consequent upon retreatment, irradiation reaction having been mistaken for recurrence. No cancer was found at autopsy. (4) Mrs. E. O. G. (23,085) died 2 years and 7 months after first therapy, of hemorrhage into the bladder from the right internal iliac vein, having developed a cecovesical fistula and a sloughing right ureter following an operative attempt to release an irradiation stricture of that ureter. No cancer was found at autopsy. (5) Mrs. R. M. (20,453) had retreatment for presumed recurrence one year after first treatment and a vesicovaginal fistula formed. She died 4 years and 2 months later of pyelonephritis, bilateral ureterostomy for strictures having been performed too late. No cancer was found at autopsy. (6) Mrs. S. W. (22,230) died 8 years and 2 months after primary treatment, of acute ulcerative cystitis, ureteritis, and pyelonephritis. No cancer was found at autopsy. She, too, had received further therapy ten months after first treatment because of suspected persistence of cancer. (7) Mrs. M. G. (19,940) died of pyelonephritis 13 years and 10 months after the start of treatment. Again irradiation reaction had been mistaken for cancer and she had been retreated. She lived fairly comfortably with essential hypertension and a rectovaginal fistula until her thirteenth posttreatment year when, within three months of an intravenous pyelography, one kidney ceased functioning. A vesicovaginal fistula formed. It was too late when cutaneous drainage of the other kidney was perceived necessary. No cancer was found at autopsy.

Complications From Irradiation.—Of those patients dying before the fifth year from treatment, proctitis occurred in 9, a rectovaginal fistula in 1, a rectovesical fistula in 1, and double fistulas in 1. Twenty-six of the five-year survivors suffered a total of 47 complications as follows: incisional hernia, 1; proctitis, 8; rectal stricture, 5; rectovaginal fistula, 5; double fistulas, 2; rectal obstruction, 2; ileitis, 1; cystitis, 18; unilateral ureteral stricture, 3; bilateral ureteral stricture, 1; and vesicovaginal fistula, 1. This simple listing does not give any information about the combination and sequence of complications, so the more serious cases are briefly summarized.

1. *Hysterectomy, radium, and x-radiation:* cystitis at 15 months, stricture of right ureter at 20 months, incisional hernia at 4 years, functionless kidney at 10 years.

2. *Radium:* double fistulas 15 months later following operation for strangulated femoral hernia, cardiovascular death at 6 years.

TABLE V. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1929 TO 1933, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	DIED FROM RADIATION BEFORE 5 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 5 YEARS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 10 YEARS	UNTRACEABLE AT 10 YEARS	DIED FROM RADIATION BEFORE 10 YEARS	ALIVE AT 10 YEARS
Untreated	5				0	0					
Amputation of cervix	1	0		0	0	1	0	0	0	0	1
Amputation of cervix and radiation	2	0	0	0	0	2	0	0	0	0	2
Hysterectomy	1	1		0	0	0					0
Hysterectomy; radiation	4	0	0	0	0	4	0	1	0	0	3
Radiation; hysterectomy	1	0	0	0	0	1	1		0		0
Radium	109	4	0	3	4	32 (29%)	2	8	0	0	22 (20%)
Radium; 200-kv. x-radiation*	153	0	4	5	0	66 (43%)	4	5	2	2	53 (35%)
Totals	276	5 (2%)	4 (2%)	8 (3%)	4	106 (38%)	7	14 (5%)	2	2	81 (29%)

*Technique of Dr. John W. Meachen (see text covering Table V).

Radium and x-radiation:

3. Proctitis at 6 months, stricture at 2 years, rectovaginal fistula at 9 years.

4. Proctitis at 7 months, rectovaginal fistula at 11 months, cystitis at 14 months, vesicovaginal fistula at 17 months.

5. Proctitis at 10 months, colostomy for obstruction at 12 months, cystitis at 23 months.

6. Proctitis at 10 months, stricture at 5 years, rectovaginal fistula at 9 years.

7. Ileitis found on abdominal exploration at 5 years, cystitis at 6 years, recurrent ileitis at 12 years.

8. Cystitis at 3 years, severe hematuria at 6 years treated by cystotomy and diathermy excision of diseased area.

9. Cystitis at one year, still present at 6 years; left hydronephrosis and functionless right kidney at 6 years and 8 months; left nephrostomy at 8 years.

10. Cystitis at 5 years, functionless kidney at 8 years. Except as stated, the above patients were alive 10 to 14 years from primary therapy.

Survival of Patients With Apparently Favorable Cancers.—According to the clinical findings, 88 patients, 32 per cent of the 276 in this group, had tumors confined to the cervix. Sixty, 68 per cent, of them comprised 57 per cent of the five-year survivors, and 50, 57 per cent, of them comprised 62 per cent of the ten-year survivors.

Late Recurrence.—One patient in this group died of proved recurrence at 13 years and 3 months, and another was alive with biopsied recurrence 13 years and 10 months after radiation. Previously[1] we had no proof of recurrence after the twelfth year. It appears that survival for 15 years may be the criterion of absolute cure for this type of cancer.

1934 to 1938 (Table VI)

During this interval there was no change in radium treatment. Two well-screened doses of 2,000 to 3,000 mg. hr. were most often employed. The total dose of x-radiation as given by Dr. Meachen did not exceed 4,800 r. and much more often was 3,200 r. or less because of a fear of complications. Since October, 1937, one of us (R. D.) has administered the x-radiation. The technique of 200-kv. therapy has been as follows: standard apparatus, 50 cm. distance, filter of 0.5 mm. copper, an average of 5 treatments through each of 3 portals,

one 15 × 15 cm. anterior and two 10 × 15 cm. posterior-oblique, for an average total dose of 6,000 r., measured with scattering, given within a period of three weeks. The technique of 1,000-kv. therapy was: 1,000 kv. constant potential, 70 cm. distance, filter of 3.0 mm. lead and 8.0 mm. copper, 15 to 18 treatments in about 3 weeks, delivered through three 10 × 10 cm. portals, one anterior and two posterior-oblique for an average total dose of 7,500 r. measured with scattering. About one-third of the patients in this series received x-radiation before radium.

Deaths From Intercurrent Disease.—The causes of the 22 deaths were: cardiovascular disease, 13 (2 had diabetes); pneumonia, 3 (one of these followed laminectomy for *perineural fibroma* of the spinal cord; no cervical cancer was found at autopsy); peritonitis, 2 (from perforated duodenal ulcer, and following operation for primary *carcinoma of the transverse colon;* no cervical cancer was found at autopsy); chronic ulcerative colitis, 1 (no cancer was found at autopsy); pulmonary embolus following chronic deep phlebitis of the leg, 1; meningitis from neglected middle-ear infection, 1; and suicide, 1. The cancers of 13 of these patients had been classified as confined to the cervix.

Deaths From Irradiation.—(1) Mrs. M. M. (28,816) died of pulmonary embolism 31 days after resection of the rectosigmoid for necrosis developing 5 months after radium. (2) Mrs. M. T. V. (24,607) died of uremia from acute necrosis of the ureters 13 months after combined radium and x-rays. Her cancer had been early. (3) Mrs. G. C. (25,694) died of pyelonephritis associated with severe irradiation cystitis 3 years and 6 months after combined treatment. (4) Mrs. I. M. O. (24,943) died of shock following resection for irradiation ileitis 4 years and 2 months after combined therapy.

Complications From Irradiation.—Minor cystitis and proctitis occurred in 6 patients who died within 5 years of first treatment. Thus far, 36 complications have developed in 27 patients who were alive at 5 years: cystitis, 15; proctitis, 9; ileitis, 3; unilateral ureteral stricture, 3; bilateral ureteral stricture, 1; vesicovaginal fistula, 2; ureterovaginal fistula, 2; and double fistulas, 1. The combination of irradiation followed by radical hysterectomy proved too stringent. Two of the patients so treated got vesicovaginal fistulas. One of them was cured by colpocleisis. A right ureterovaginal fistula and a stricture of the left ureter ensued in another who lost her left kidney and now has a ureterostomy. Right ureterovaginal fistula in another was treated by ureterosigmoidostomy. Of those treated with radium and x-rays before November, 1937, two came to cystotomy and excision of necrotic bleeding tissue. The bilateral ureteral strictures of one patient relaxed without interference. Colostomy and later colpocleisis were a satisfactory solution for the patient with double fistulas. The stenosed ureter in another was effectively dilated from above at the time a temporary nephrostomy was made. Operation was successful in the three cases of ileitis, resection having been performed twice and lateral anastomosis around a localized lesion once. Radiation with 200-kv. x-rays from the fall of 1937 through 1938 has resulted thus far in one case of severe hematuria which cleared with repeated transfusions of whole blood. One patient treated with 1,000-kv. x-rays lost one kidney from pyelonephritis due to stricture of a ureter. She had, however, been overtreated with radium, receiving 7,500 mg. hr.

Incidence of Favorable Cancers.—One hundred and thirty patients, 40 per cent of this series, had tumors that seemed to be limited to the cervix. Ninety-five, 73 per cent of them, comprised 67 per cent of the 142 five-year survivors. Thus, between 1934 and 1938 there was a larger percentage of patients with a good prognosis and proportionately more of them were alive at five years. The disturbing revelation is that there was a smaller percentage of five-year survivors among those with more advanced cancers. It appears that the decreased incidence of complications in this series resulting from a reduction in the amount of x-radiation was accompanied by a failure to save more patients with a poor prognosis.

Cases With Other Tumors.—At the time of cervical treatment one patient in this group had a primary *carcinoma of the breast* and another had widespread peritoneal involvement with *papillary adenocarcinoma of unknown origin* (her cervical growth was epidermoid). Two other cases of double primary tumors are included above among those dying from intercurrent disease. One of the five-year survivors had a *papilloma of the bladder* removed by fulguration two years after treatment of her cervical cancer and a primary *carcinoma of the bladder* removed at 4 years and 6 months. (We have now encountered three primary cancers of the urinary bladder in patients previously irradiated for cancer of the cervix or endometrium.) A primary *carcinoma of the ovary* was removed from another patient five years after radiation for cancer of the cervix.

TABLE VI. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1934 TO 1938, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	DIED OF INTERCURRENT DISEASE BEFORE 5 YEARS	DIED FROM RADIATION BEFORE 5 YEARS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS
Untreated	12		0		0	0
Amputation of cervix	1	0	0	0	0	1
Amputation of cervix; radium; x-radiation*	1	0	0	0	0	1
Hysterectomy	5	0	1		0	4
Hysterectomy; radium	3	0	1	0	0	2
Hysterectomy; x-radiation*	3	0	0	0	1	2
Radium; x-radiation*; hysterectomy	16	1	0	0	0	8
Radium	32	1	1	1	0	17 (53%)
Radium; 200-kv. x-radiation*	191	0	15	3	0	76 (40%)
Radium; 200-kv. x-radiation†	41	0	1	0	1	19 (46%)
Radium; 1,000-kv. x-radiation‡	23	0	3	0	0	12 (52%)
Totals	328	2 (0.6%)	22 (7%)	4 (1%)	2	142 (43%)

*Technique of Dr. John W. Meachen. Cases treated to November, 1937.
†Technique of Dr. Richard Dresser (see text covering Table VI).
‡Technique of Dr. Richard Dresser (see text covering Table VI).

TABLE VII. COMBINED RESULTS

PERIOD	NUMBER OF CASES	ALIVE AT 5 YEARS	ALIVE AT 10 YEARS	ALIVE AT 15 YEARS	ALIVE AT 20 YEARS	ALIVE AT 25 YEARS	ALIVE AT 30 YEARS
1902-13	83	10, 12%	6, 7%	6, 7%	6, 7%	4, 5%	4, 5%
1914-18	79	15, 19%	9, 11%	7, 9%	5, 6%	3, 4%	
1919-23	119	27, 23%	14, 12%	10, 8%	7, 6%		
1924-28	226	64, 28%	48, 21%	35, 15%			
1929-33	276	106, 38%	81, 29%				
1934-38	328	142, 43%					
Totals	1,111	364, 33%	158, 20%	58, 11%	18, 6%		

Total Salvage (Table VII)

As is apparent from Tables I to VI, no statistical corrections have been calculated. The figures for results are as low as can be made and their improvement over the years reflects better treatment despite the errors of commission and omission which will be discussed below. The results with radium and 200-kv. x-radiation in patients treated from January, 1934, to November, 1937 (Table VI), were not so good as those in the 1929 to 1933 group. This is attributed to the reduction in the amount of x-rays because of the fear of complications and a consequent failure to save some patients with more advanced cancers.

Carcinomas of the Cervical Stump

Fifty-eight patients, 5.2 per cent of the whole series of 1,111, had had a supravaginal hysterectomy performed prior to the diagnosis of cervical cancer. Furthermore, 15 patients had had previous bilateral oophorectomy and 8 had had bilateral salpingo-oophorectomy. Five more had had bilateral salpingectomy and two had had both tubes ligated. Thus, 30 patients, 2.7 per cent of the series, developed cancer in the cervix of a uterus that had been rendered a

completely useless organ or one capable only of menstrual function. The implication of these figures is clear.

Discussion

Deaths and Complications From Irradiation.—As might be expected, thin patients have more often had complications than stout. A review of the damage done by therapy (*v.s.*) reveals the following errors:

1. *Overtreatment.*—We now consider anything over 5,400 mg. hr. given in one application and anything over 6,000 mg. hr. given in two applications an overdose of radium. As we use radium, that is, with essentially all beta radiation screened back, we have learned not to leave any amount of it in for over thirty hours unless the indications of the situation outweigh the practical certainty of complications. Despite these restrictions, excessive damage will ensue in some patients even if x-rays are not administered. The maximum relatively safe amount of 200-kv. x-radiation, when combined with the above dose of radium, is 6,000 r., measured with scattering, about one-third of which is delivered to the center of the pelvis. According to our experience thus far, it appears that the maximum relatively safe dose of 1,000-kv. x-radiation is about 7,200 r., measured with scattering, about one-half of which is delivered to the center of the pelvis. The maximum relatively safe daily dose of x-radiation is 400 r. We feel, but have not proved, that it is better to give all radiation within six weeks and to administer x-ray therapy first except in cases with hemorrhage, which is more quickly controlled by radium. If the above amounts of radium and x-rays do not destroy a given cancer, it is likely that more will be ineffective. Of course we are constantly made aware that some patients can tolerate more irradiation than others and that some cancers respond better than others to the same dosage.

2. *Retreatment.*—Mistaking irradiation reactions, viz., edema of the broad ligaments, shaggy rectal ulceration, and perirectal, rectovaginal, and vesicovaginal thickening for persistent cancer, and giving further treatment has been a serious error of the past, although it is impossible to be certain that some retreatments may not have destroyed residual cancer. In general, retreatment is only occasionally really beneficial and, at that, usually only for local vaginal recurrences. Hence it is safer to withhold additional therapy unless the evidence for recurrence is convincing.

3. *Pelvic Surgery by the Abdominal Route After Heavy Irradiation.*—One death in the 1929 to 1933 group followed an attempt to release a stenosed ureter. Another patient in this group developed a ureteral stricture and later lost the function of its kidney from the combination of radiation and hysterectomy. One of the deaths in the 1934 to 1938 group was due to severe local sepsis followed by embolism, resection of the rectosigmoid having been performed after radium. It would have been safer to perform a colostomy. In 1936 one of us (G. V. S.) tried the combination of preoperative irradiation with half the usual amounts of radium and x-rays and then radical hysterectomy. The above-described complications made it seem wiser to give up the experiment.

4. *Delaying Operative Interference in the Hope That Complications Would Improve Spontaneously.*—In retrospect it seems that nearly all the deaths we have attributed to radiation could have been prevented by timely colostomy and/or diversion of the ureters. Since most of the deaths and potentially lethal complications were due to ureteral damage, the development of irradiation

reactions is a signal for repeated intravenous pyelography and preparedness for surgery as long as the patient lives. We now know that ureteral stenosis can occur quickly and at any time up to fifteen years after treatment.

Treatment of Irradiation Complications.—While patients are being irradiated we have in recent years made it a point to increase their vitamin intake, especially of thiamine chloride, but cannot state that they have had less radiation sickness therefrom because the amount of such disturbance varies so much anyway in different patients. Acute postradiation pelvic inflammations have been the cause of nearly all our immediate and early deaths. Fortunately, these have been fairly rare, but we have not yet treated them successfully. Because perforation of the lower bowel is very likely involved, we think pelvic drainage and colostomy may be salutary, along with the modern antibacterial drugs. *Irradiation proctitis:* The tenesmus and pain, though usually of less than two months' duration, are difficult to relieve. One-grain opium suppositories inserted high in the rectum seem to be as effective as anything, along with the maintenance of soft stools. For the usual, not alarming bleeding, iron, liver and high-vitamin diet are prescribed. For the rare profuse and prolonged rectal bleeding, we have found repeated transfusions of whole blood best. The later strictures are gently dilated if they are causing partial obstruction in spite of careful catharsis and the patients are taught to maintain dilatation with a test tube.

Irradiation cystitis: We know of nothing that will hasten its regression or prevent recurrence, but at present are trying frequent instillations of purified cod-liver oil. The patients are given general and symptomatic treatment and watched both for ascending infections and ureteral blockage. Severe and recurrent hematuria is more easily controlled by bed rest and whole blood transfusions than by operative procedures.

Vesicovaginal fistula from irradiation: In a very small experience, colpocleisis has been more successful than direct closure.

Rectovaginal fistula from irradiation: Attempts at closure have failed. Although those who have had colostomy realize how much more satisfactory it is, most patients refuse the operation.

Double fistulas: Providing the ureters are functioning normally and the anal sphincter is competent, our experience with one case indicates that colostomy and later colpocleisis are good procedures. Left transverse loop colostomy is easier to perform than those lower down and just as satisfactory.

Ureteral stricture: Beginning hydro-ureter and hydronephrosis pose a difficult problem. Should immediate attempts at dilatation be understaken? Irradiation cystitis may make it impossible to find the ureteral orifices. The trauma of cystoscopic dilatation may cause complete blockage, yet dilatation has been apparently successful in a few instances. On the other hand, spontaneous cure has been observed, even when bilateral stenosis was present. If one ureter is functioning normally and the other is becoming progressively stenosed, would it not be better to sacrifice the kidney than to risk the dangers of implanting a pathologic ureter into the bowel or to give the patient the burden of a cutaneous ureterostomy or nephrostomy? Furthermore, implantation into the intestine may be interdicted by proctitis or a rectovaginal fistula. Repeated study and weighing the above considerations in relation to age, general condition, and cancer prognosis will point to the best management. Evidence of renal infection or a rise in blood nonprotein nitrogen mean that the period of expectancy must be terminated.

Status of Treatment.—Bonney,[2] who has reported on the largest number of radical operations in recent years (500, of a total series of about 800 cases), had 70 operative deaths. This figure, which does not include deaths from complications or their treatment, is considerably larger than that for all the deaths in the above series (surgery, 16 postoperative deaths and 2 later deaths from intestinal obstruction; radiation, 8 early and 11 later deaths) plus the 19 patients with potentially lethal complications who were alive 5 to 15 years after primary therapy. Though we believe, but have not been able to ascertain, that radiation caused or hastened more deaths than we have listed above from that cause, we are sure they would not make the above total mortality even approximate his. In his 300 most favorable cases he had 30 operative deaths. After performing

radical surgery, one of us (G. V. S.) is always left with a feeling of dissatisfaction because the anatomy of the pelvis makes a true "bloc" resection impossible. It might be argued that pelvic metastases can be eliminated only by surgery. Although irradiation has not been proved capable of destroying pelvic metastases, the greater total salvage in consecutive cases coincident with the increased use of radium and x-rays is circumstantial evidence that it may do so.

Of necessity one must resort to the radical operation in instances of operable, radioresistant cancers. There was only one such in this series so far as we could determine. At the Free Hospital for Women the radical operation is still occasionally performed, because it is requested, for purposes of instruction, perhaps unconsciously as an exercise of surgical prowess, as a reaction to a run of irradiation complications or because other pelvic tumors, inflammation or endometriosis make it preferable to radiation. In cases of very early cancer, viz., where the diagnosis is equivocal until biopsy, simple complete hysterectomy is likely to be performed to avoid radiation complications, with the exception of endocervical tumors, which so often are more advanced than apparent from examination. In some of those very early cases we have found less than the usual amounts of radium safe and curative, both with and without x-rays, but this procedure leaves a feeling of uncertainty. The facts derived from the above series again lead to the conclusion that for the great majority of patients the best treatment is a combination of radium and x-rays given in maximum relatively safe amounts, even at the cost of a small number of deaths and a large incidence of complications.

Summary

Eleven hundred and eleven consecutive, previously untreated, pathologically confirmable cases of cancer of the uterine cervix are reviewed. The percentages of patients who were alive five years after first treatment are as follows: 1902 to 1913, 12; 1914 to 1918, 19; 1919 to 1923, 23; 1924 to 1928, 28; 1929 to 1933, 38; 1934 to 1938, 43. The percentages of patients alive at ten years in the same groups to 1934 are: 7, 11, 12, 21, and 29. The percentages of patients alive at fifteen years to 1929 are: 7, 9, 8, and 15. The improved results are due for the most part to the use of radium and x-rays. Seventy-one per cent of the patients alive five years after treatment were alive at ten years, and 75 per cent of those alive at ten years were alive at fifteen years.

Two patients had proved recurrence between thirteen and fourteen years after irradiation.

Deaths, early and late, from treatment and intercurrent disease are listed. Complications and their treatment are given considerable attention, since they are such an important part of radiation therapy.

Four patients had another primary cancer at the time that of the cervix was treated and six later developed primary malignancies, two of which occurred in organs previously irradiated, namely, bladder and rectum.

Of the whole series of 1,111 patients, 5.2 per cent had had a previous supravaginal hysterectomy and 2.7 per cent more had had tubes or ovaries or both removed or tubal ligation.

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A TRANSPLANTABLE RAT TUMOR*

RUTH M. WATTS, PH.D., AND FRED L. ADAIR, M.D., CHICAGO, ILL.
(From the Department of Obstetrics and Gyecology, The University of Chicago)

IN VIEW of the relationship of hormones to tumor formation and its bearing upon clinical problems, it seems worth while to report the occurrence of a transplantable rat tumor arising in a colony of ovariectomized rats used for the assay of estrogens. Although there is no direct evidence that the tumor arose as the result of the administration of estrogen, this possibility is supported by the higher incidence of tumors and tumorlike growths in this colony than in the stock colony. The use of estrogen in this colony varied from the procedure commonly employed in producing tumors experimentally in that the estrogen was administered in physiologic doses intermittently over a long period rather than in a high dosage or by continuous treatment. According to Lipschütz the factor of timing is important in the production of tumors with estrogens. Much of the work on the relation of estrogens to tumor development has been concerned with mammary and connective tissue tumors, and often large doses of estrogens have been given for prolonged periods. The occurrence of spontaneous tumors in rats has been reviewed by Curtis, Bullock, and Dunning,[1] McEuen,[2] Ratcliffe,[3] Jenney,[4] and others. Various rat sarcomas have been found to be transplantable. McEuen[5] has reported the occurrence of cancer in rats treated with estrone and has transplanted a spindle-cell tumor through 15 generations.

Our transplantable tumor is a sarcoma. It arose in the mesentery, but not in the usual site of the lymphosarcomas of the lymph nodes at the ileocecal junction. It was readily transplanted by transfer of a fragment of tissue or by the inoculation of a suspension of tissue and has been carried through 24 generations. It showed a high incidence of successful transfer. The transplanted tumor grew rapidly and more than half of the hosts failed to survive thirty days.

This work was undertaken not only because of our general interest in the field of the relationship of hormones to tumor formation[6-8] but also in hope that an ovarian tumor might be induced which could be used to further our study on the relation of hormones to ovarian tumors.[6]

History of Rat Colony and Tumor Incidence

Stock Colony.—The colony of rats in which this tumor arose and with which it was continued was a Wistar strain which had been carried on in this laboratory since 1930 without interbreeding with other strains. The diet consisted of a modified Steenbock diet supplemented with bread, milk, ground beef, and lettuce, but later the stock rats received calf meal.

Assay Colony of Ovariectomized Rats.—A colony of adult ovariectomized rats was maintained for the purpose of assaying estrogens in

*This work has been done under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

the course of other investigations on the methods of assay of estrogens, excretion of estrogens in toxemia of pregnancy,[9] and occurrence of estrogens in ovarian cyst fluids.[6, 7] During the period 1934 to 1941 there was a total of more than 800 rats in this group. At the time of castration these rats weighed, on the average, 160 grams. Protocols on these animals include the dosage and preparations administered, dates of injection, response, and disposal of the animal. These rats received crystalline estrone, extracts of pregnancy urine and ovarian cyst fluids, usually administered subcutaneously in olive oil but occasionally as aqueous preparations. The rats received physiologic doses of these substances. After a positive response an animal was not used again for two weeks; after a negative response it was used the following week; after two negative responses it was given a priming dose of approximately 2 rat units of estrogen (pregnancy urine extract). Assay rats were used for about one year. As rats became irresponsive or old the assay colony was replenished with young rats. When the need for the colony diminished the last group was retained longer than usual. In this final group three malignant-appearing tumors were found. These will be discussed later.

Tumor Incidence.—In reviewing the disposal records of the breeding and stock colony, 32 instances (2.8 per cent) of tumors were recorded in 1,144 records. Of these, 18 (56.3 per cent) were mammary tumors and 4 (12.5 per cent) were intraperitoneal tumors. None was similar to the transplantable tumor which is the subject of this report.

In reviewing the protocols of the entire assay colony it was noted that of the 743 with autopsy records, 47 (6.3 per cent) had developed tumors or tumorlike growths. These were as follows: 14 subcutaneous at the injection site, 10 in the region of the neck, 8 intraperitoneal, 4 kidney, 2 vaginal, 1 each, mammary, adrenal, and thoracic cavity, 5 gastrointestinal tract, and 1 "oil cyst."

The subcutaneous growths appeared usually as lumps at the injection site and were sometimes associated with small "oil cysts." They were either cystic, firm fibrous tissue or friable malignant-appearing tissue. They attained sizes as great as 4 by 5.5 by 6 cm. One of these tumors was transplanted (see Rat FP 0.13[5] below). The intraperitoneal tumors were of a miscellaneous nature. One of these (Rat FP 03[8]) is the subject of this report and one other (Rat FP 0456[4]) is described below.

The incidence of pathology was somewhat higher than in the stock colony. At no time was there any evidence in either colony of tumors of a parasitic or infectious origin, and no spontaneous sarcomas were observed such as described by McEuen[5] and Jenney.[4]

Transplantation of Tumors.—One tumor in a stock rat and three tumors arising in this assay colony of ovariectomized rats appeared to be malignant and were tested by transplantation.

Rat FP 03[8].—The tumor arising in the mesentery of this ovariectomized rat is the subject of this report and will be discussed in detail. The tumor was easily transplanted and was transferred through 24 generations within twenty-seven months.

Rat FP 0456[4].—This ovariectomized rat had two subcutaneous cysts on the back in the region of the injection site, and a tumor approximately 1 by 2 by 4 cm. adjacent to, and partially obliterating, the caudate lobe of the liver. Both the liver tumor and the subcutaneous tumor resembled in every way the tumors observed from the transfer of the tumor found in Rat FP 03[8]. Twenty-two milliliters of ascitic fluid were obtained. The liver tumor was transferred by the emulsion technique through three generations but the one tumor transferred to the fourth generation failed to "take." The tissue resembled a sarcoma.

Rat FP 013[5] was an assay rat with a subcutaneous tumor 1 by 2 by 2 cm. This tumor was composed of numerous locules, some of which contained a milky fluid. The tissue varied from nodular firm tissue to

friable hemorrhagic tissue and appeared to be malignant. Microscopically it resembled the sarcoma of Rat FP 03[8] and the tumor of Rat FP 0456[4]. Three transfers of this tumor were not successful.

Rat FP 25[13] was a female rat from the breeding colony. The tumor arose in the vagina and microscopically it did not resemble the tumors which appeared in the assay rats. All three of the primary transfers were successful but 16 transfers in the second generation failed.

Description of Tumor

History of Host.—A normal young adult rat, FP 03[8], was bilaterally ovariectomized, and after twelve days estrogen injections were begun. Within the next seventy-two weeks the rat received 51 injections of estrogen in oil; of these, 11 were crystalline estrone, 23 pregnancy urine, 17 "priming doses" of pregnancy urine extract, and one an extract of ovarian cyst fluid. Twenty-four extracts gave positive responses and 27 negative. Injections were such that a positive response was obtained every second or third week. Two weeks after the last injection the rat was sacrificed because of a large tumor distending the abdomen.

Gross Description.—The tumor arose in the mesentery and invaded the intestinal wall. It did not arise in the lymph nodes at the ileocecal junction. The tumor measured 5 by 5 by 5 cm. It was irregular in shape and showed cystic structures two of which contained 37 ml. and 45 ml. of watery fluid, respectively. Some of the solid portions were hemorrhagic friable tissue and others pale yellow friable tissue which was somewhat translucent.

Microscopic Description of Original.—Fig. 1 is a photomicrograph (x370) of the portion of the tumor from which tissue was taken for the original transfers. The cellular structure is uniform and resembles a round-cell sarcoma. The cells stain deeply with hematoxylin and eosin stain and often show many stages of mitotic division. There is a characteristic tendency for a rosettelike arrangement of the cells. Fig. 2 is the same microscopic section as shown in Fig. 1 but at x450 magnification. While the exact character of the tumor may be questioned, morphologically it appears to be a sarcoma.

Microscopic Examination of Transferred Tumor.—More than 160 microscopic examinations have been made of transferred tumor tissue, representing tumors in various sites and in the eleven lines carried on from the original tumor. All lines were similar. Irrespective of the site of the tumor, the tissue characteristics remained constant through 24 generations. Neither variations in the cell picture nor any tendency to change of type were observed. The tissues were fixed in Zenker's solution and stained with hematoxylin and eosin. Tumor Line 2 was followed microscopically in 24 generations. The photomicrographs of the original tumor are shown in Figs. 1 and 2; the tenth generation and the twentieth generation of Line 2 are shown in Figs. 3 and 4, respectively.

Transplantability.—It was possible to transfer this tumor by implantation of fragments of tissue or by the injection of a suspension of tissue. This was accomplished either subcutaneously or intraperitoneally. The tumor was carried on in eleven lines: three lines were followed for 10 generations, one for 12, one for 17, one for 19, two for 21, two for 22, and one for 24. The tissue characteristics remained the same, but the ease of transfer increased with repeated transfers. No line died out spontaneously and no regression of the tumor was ever observed. There was no evidence that the tumor was infectious in nature and it never appeared elsewhere in the colony. Cultures of the tumor tissue were negative and the tumor was transmitted only by inoculation or transplantation of tissue. The tumor invaded other tissues but there were no proved instances of metastases. However, more than half of the hosts died within less than thirty days after receiving a transfer of the tumor tissue.

Bacteriologic Examination

In order to rule out the possibility of an infectious nature of the tumor and the subsequent transmission in this way, bacteriologic examinations* have been made of the tumor tissue. Fifteen tumor hosts

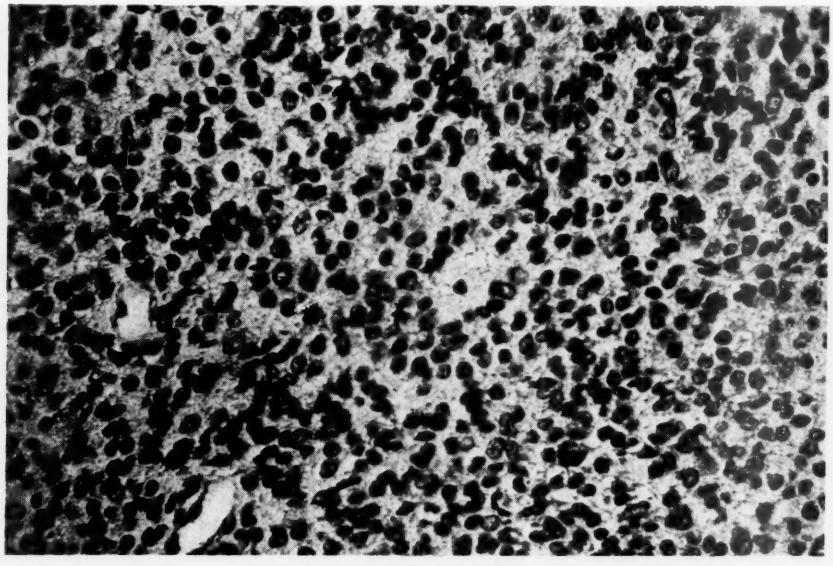

Fig. 1.—Original tumor from the mesentery of Rat MP 03^8. (×370.)

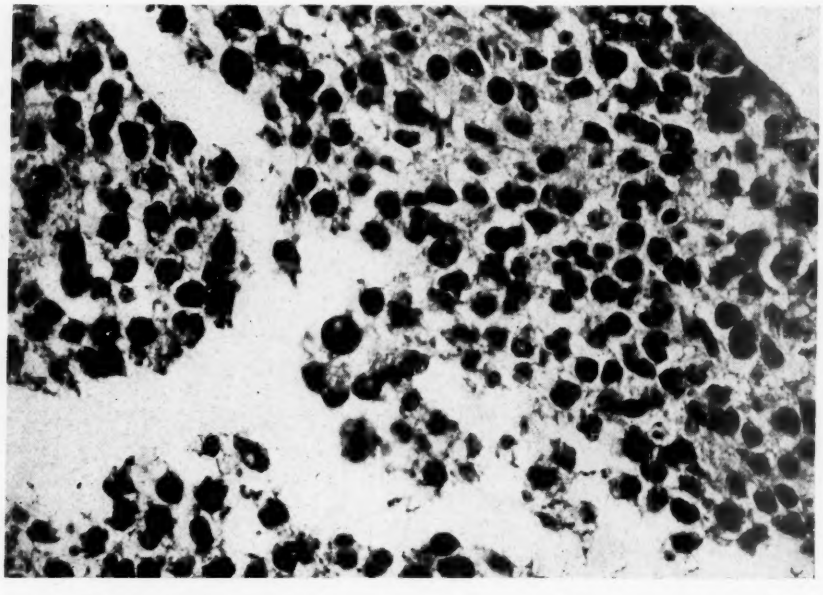

Fig. 2.—Original tumor from the mesentery of Rat MP 03^8. Same microscopic section as shown in Fig. 1. (×450.)

have been examined. Twenty-three examinations were made of the tumor tissue from tumors in various states of development or from different parts of the same tumor. Nine specimens of ascitic fluid were examined. The ages of the tumors, as represented by the time elapsing after the transfer of the tumor tissue to the host, were 8, 8, 13, 17, 20,

*We are indebted to Dr. Lucile Hac for these examinations.

24, 29, 30, 31, 45, and 49 days. The generations represented were 11, 14, 15, 16, 17, 18, 20, and 21. No organisms were found in direct smears made from the tumor tissue or the ascitic fluid and stained with Gram's or acid-fast stains. Cultures made on blood agar plates and in Rosenow's brain broth medium showed no growth.

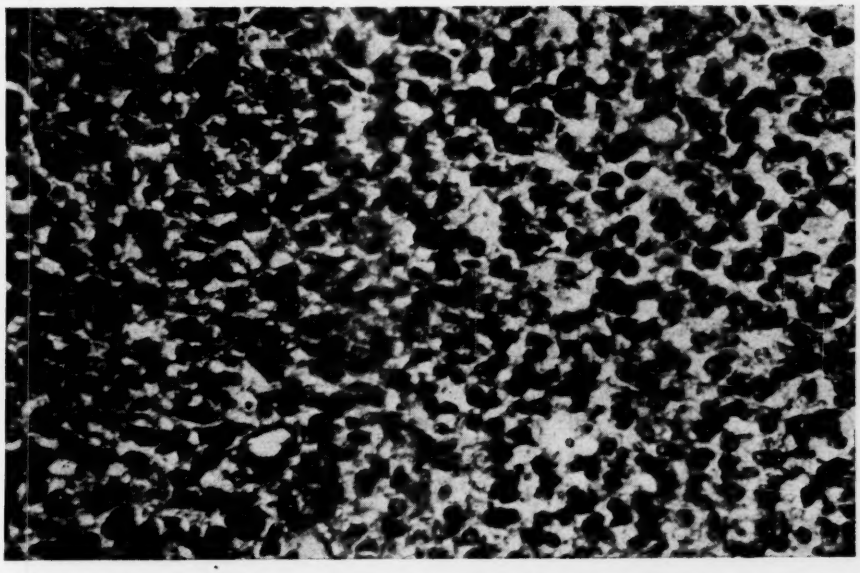

Fig. 3.—Peritoneal implant in Rat MP 347 twenty-eight days after transfer. Generation 10 of Line 2. (×335.)

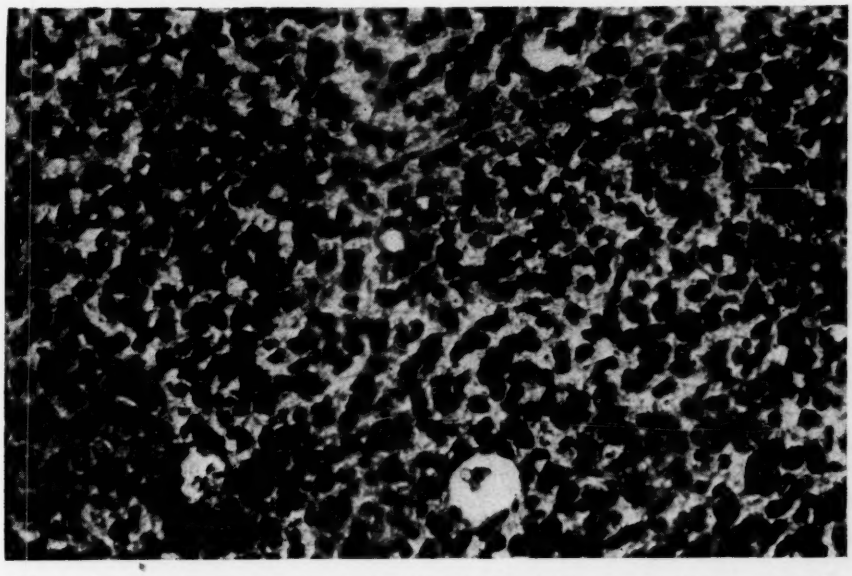

Fig. 4.—Omental tumor in Rat MP 136[2] twenty-two days after transfer. Generation 20 of Line 2. (×335.)

Filtrates From Tumor Tissue

In studying the nature of the transmission of the tumor, filtrates were made from the tumor tissue. In the first experiment a suspension of an omental tumor was used and the filtrate prepared by filtration through a Berkefeld filter "V." Three rats received filtrate equivalent

to 200 mg. of tissue and showed no evidence of tumor growth at autopsy. In control groups, all three rats receiving 200 mg. of tissue, two of three rats receiving 100 mg., and two of three rats receiving 25 mg. developed tumors. Three of four rats which received tissue suspension equivalent to 100 mg. of tissue, but which was incubated for five hours at room temperature, developed tumors also.

In the second experiment a filtrate of a tumor enveloping the caudate lobe of the liver was prepared by filtration of a suspension of tissue through a Pyrex sintered glass filter ("fine"). One rat received an amount of filtrate equivalent to 50 mg. of tissue and one an amount equivalent to 100 mg. of tissue; both failed to develop tumors. Three of the four controls which received 100 mg. of tissue developed tumors.

In the third experiment the filtrate was made from an omental tumor by filtration through a "fine" Pyrex sintered glass filter. The four rats receiving 100 mg. of tissue developed tumors, but 3 receiving filtrate equivalent to that amount of tissue were all negative.

In the fourth experiment the filtrate was obtained by passing a suspension of an omental tumor through a Berkefeld filter "V." Three pairs of control rats received amounts of tissue suspension containing 10, 25, and 100 mg. of tissue, respectively, and all developed tumors. Two rats received filtrate equivalent to 100 mg. and two equivalent to 200 mg. of tissue, and these were all negative.

Since no tumors developed from either of these filtrates, it would seem that the factor producing these tumors was not present in a sterile filtrate obtained from Berkefeld filtration or in a cell-free, nonsterile filtrate passed through the sintered glass filter.

Techniques of Transfer

Hosts.—The hosts were selected with respect to sex, weight, and age. In routine transfer of the tumor three adult hosts were used.

Tissue Transfer Method.—The first transfers of the tumor were made by implantation of small fragments of tissue, approximately 2 by 2 by 2 mm. The transfers were made either by implanting subcutaneously or by embedding in the ovarian fat using sterile technique. This method was employed only in the early work.

Tissue Suspension Method.—A weighed amount of tissue was macerated with fine-tipped surgical scissors, using aseptic conditions, until it would pass through a No. 19 hypodermic needle. This macerated tissue was suspended in a known amount of physiologic saline solution so that 1 or 2 ml. of suspension contained the required amount of tissue to be inoculated. The amount of tissue transferred varied, and amounts as low as 0.5 mg. were used. In the routine transfers, 100 mg. of tissue were used. This amount was undoubtedly excessively large but since this amount was adopted as a standard procedure early in the investigation, it was continued for uniformity. Transfers were usually not made until the host died or was sacrificed because of a terminal condition.

Incidence of Successful Transfer

The incidence of successful transfer of the transplanted tumor is shown in Table I. The data have been compiled in regard to the sex but not the age of the host, and as to whether or not a weighed amount of tissue was transferred. In early work the tissue transferred was not weighed, but the amounts were comparable to those used later. In general, the hosts were adult, and three rats were used for each tissue transfer. The transfers were all made by intraperitoneal injection of a sus-

pension of tissue as described above. Of the 1,171 transfers, 839 (71.7 per cent) were successful, irrespective of the amount of tissue inoculated. Of the 764 transfers made to male hosts, 550 (72.0 per cent) were successful, and of the 407 transfers made to female hosts, 289 (71.0 per cent) were successful. In the group in which transfers were made with weighed tissue, 444 (76.4 per cent) of the 581 males and 195 (73.9 per cent) of the 264 females developed tumors. In routine transfer of the tumor, 100 mg. of tissue were transferred. These data appear also in Table I. Three hundred and fifty-three (81.0 per cent) of the 436 transfers were successful. Of the 318 male hosts, 257 (80.8 per cent), and of the 118 female hosts, 96 (81.4 per cent) developed tumor. These data form the basis for Table II, but the incidence of "takes" differs slightly because only hosts allowed to survive at least thirty days are included, and hosts receiving three tissues which gave entirely negative responses are excluded. The data for males are based on 105 tumor tissues and for the females on 44 tissues. The data indicate that there is no sex difference in respect to the incidence of successful transfers.

TABLE I. INCIDENCE OF SUCCESSFUL TRANSFERS

TUMOR TISSUE		MALES			FEMALES			TOTAL		
TRANSFERS	NO.	NO.	NO. POSITIVE	% POSITIVE	NO.	NO. POSITIVE	% POSITIVE	NO.	NO. POSITIVE	% POSITIVE
Amount weighed	181	581	444	76.4	264	195	73.9	845	639	75.6
Amount not weighed	113	183	106	57.9	143	94	65.7	326	200	61.3
Total	294	764	550	72.0	407	289	71.0	1,171	839	71.7
100 mg.	137	318	257	80.8	118	96	81.4	436	353	81.0

TABLE II. SURVIVAL PERIOD OF HOSTS RECEIVING 100 MG. OF TUMOR

	MALE HOSTS			FEMALE HOSTS			TOTAL GROUP		
	NO.	%	% OF POSITIVE GROUP	NO.	%	% OF POSITIVE GROUP	NO.	%	% OF POSITIVE GROUP
POSITIVE TRANSFERS									
Survival Period									
0-19 days	31	11.4	13.5	12	10.9	13.6	43	11.2	13.5
20-29 days	101	37.0	43.9	35	31.8	39.8	136	35.5	42.8
30 or more days	98	35.9	42.6	41	37.3	46.6	139	36.3	43.7
Total	230	84.3	100.0	88	80.0	100.0	318	83.0	100.0
NEGATIVE TRANSFERS	43	15.7		22	20.0		65	17.0	
TOTAL	273	100.0		110	100.0		383	100.0	

Survival Period of Tumor Hosts

The survival period of tumor-bearing rats is shown in Table II. In this group, 383 rats received intraperitoneal inoculations of 100 mg. of tumor tissue and were allowed to survive at least thirty days. Of this group, 318 rats (83.0 per cent) showed successful transfers. Of the 273 transfers made to male hosts, 230 (84.3 per cent) were successful, and of the 110 transfers made to female hosts, 88 (80.0 per cent) were successful. These transfers were made from 127 tumors; three tissues which did not "take" have been omitted. Of the entire group of 383 hosts, 43 (11.2 per cent) survived less than twenty days after inoculation with tumor tissue, 136 hosts (35.5 per cent) survived between twenty and twenty-nine days, 139 hosts (36.3 per cent) survived longer than thirty days, and 65 hosts (17 per cent) were negative. The survival period has been determined by the death of the host or by a terminal condition necessitating sacrificing the animal.

In the group of 318 successful transfers, 43 hosts (13.5 per cent) survived less than twenty days, 136 hosts (42.8 per cent) survived

twenty to twenty-nine days, and 139 hosts (43.7 per cent) survived more than thirty days. The survival period is dependent not only upon the extent and involvements of the tumor but also upon the location and character of the tumor and the ease with which it ruptured causing extravasation of blood and exsanguination of the host.

Sites of Tumor Development

In determining the incidence of the sites of tumor development, a group of 179 hosts surviving less than thirty days has been used. This is the same group that appears in Table II. The hosts all received intraperitoneal inoculations of a suspension of 100 mg. of tumor tissue. One hundred and twenty-seven tumors were transferred. The tumors which were transferred occurred in the following sites: omentum 76, liver site 25, mesentery 14, genital fat 7, diaphragm 2, peritoneal implant 1, thoracic cavity 1, region of the kidney 1. The microscopic appearance of the tissue was the same regardless of the site of the tumor.

TABLE III. INCIDENCE OF SITES OF TUMORS IN HOSTS SURVIVING LESS THAN THIRTY DAYS

	NO. OF TUMORS IN HOSTS SURVIVING		INCIDENCE	
	LESS THAN 20 DAYS	20-29 days	TOTAL NO. OF TUMORS	IN HOSTS %
TUMOR SITES				
Omentum	43	133	176	98.3
Liver site	40	131	171	95.5
Genital fat	40	116	156	87.2
Mesentery	36	113	149	83.2
Implants				
Peritoneum	33	95	128	71.5
Xiphoid process	18	52	70	39.1
Diaphragm	24	67	91	50.8
Subcutaneous	13	40	53	29.6
Intestinal tract	6	17	23	12.8
Kidney region	2	6	8	4.5
Kidney	0	6	6	3.4
Spleen	0	4	4	2.2
Thoracic cavity	0	3	3	1.7
Stomach	0	1	1	0.6
Total number of sites	255	784	1,039	
NUMBER OF HOSTS	43	136	179	

The various sites where tumors developed are enumerated in Table III and include the omentum, liver site (liver and regions adjacent) genital fat, mesentery, intestinal tract, kidney, spleen, stomach, diaphragm, implants on the peritoneal wall, implants over the xiphoid process, along the back near the kidney, thoracic cavity and subcutaneous tissue. According to this classification, 1039 tumor sites were observed in the 179 hosts which failed to survive thirty days. The incidence of tumors in these various sites is shown in Table III. The highest incidence is in the omentum: 176 of 179 hosts (98.3 per cent) developed omental tumors. Tumors of the liver, around the liver, or growing between the lobes were found in 171 hosts (95.5 per cent). One hundred and fifty-six hosts (87.2 per cent) were found to have tumors involving or replacing the fat associated with the genital organs. Sites other than those listed have been observed, but with amounts of inoculated tissue other than 100 mg. Among those tumors were tumors of the ovary, testis, uterus, seminal vesicle, thymus, lymph nodes, heart, and lung.

The incidence of the number of different sites in which the tumors developed is shown in Table IV. The greatest number of different sites observed in one host was ten. The highest incidence was shown for seven sites. Twenty-six and three-tenths per cent of the hosts showed tumors in seven sites; 87.1 per cent showed tumors in four to eight sites; 89.9 per cent had tumors in more than three sites.

TABLE IV. INCIDENCE OF NUMBER OF SITES OF TUMOR IN HOSTS RECEIVING 100 MG. TISSUE AND SURVIVING LESS THAN THIRTY DAYS

NO. OF SITES	INCIDENCE	
	NO. OF HOSTS	%
1	3	1.7
2	3	1.7
3	12	6.7
4	23	12.8
5	27	15.1
6	40	22.3
7	47	26.3
8	19	10.6
9	4	2.2
10	1	0.6
Total	179	100.0

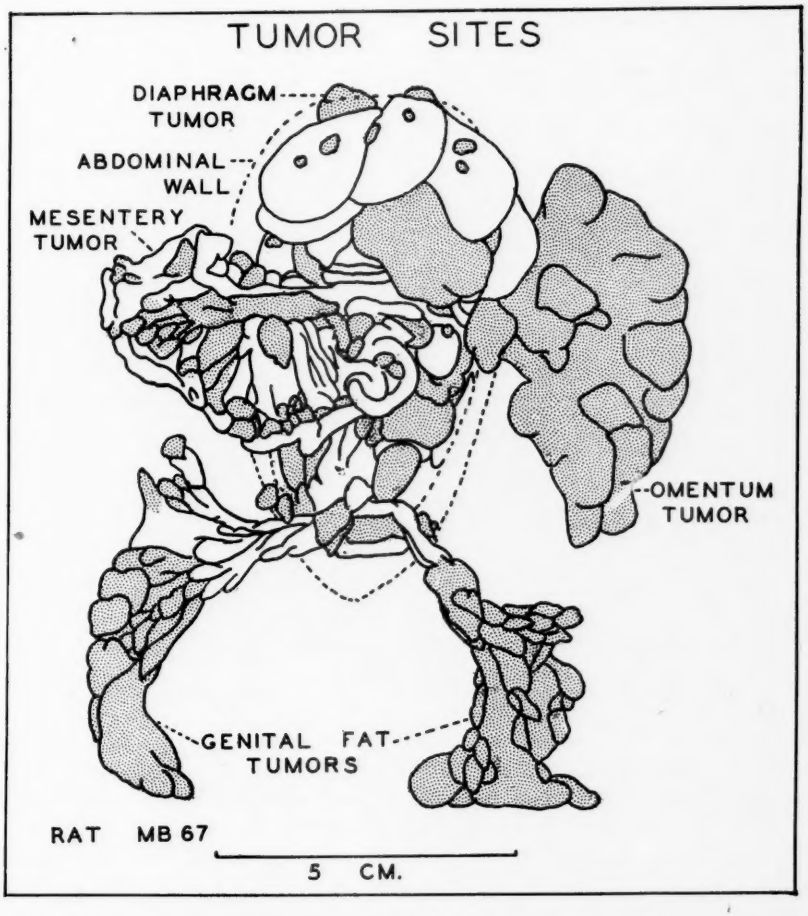

Fig. 5.—Sites of tumor formation. Drawing of Rat MP 67 twenty-one days after intraperitoneal transfer of a suspension of tumor tissue. Tumors are represented by shaded areas.

The sites of the tumor development are illustrated in the drawing of Rat MB 67, Fig. 5. This rat was sacrificed twenty-one days after inoculation because of a terminal condition. The abdominal cavity was distended with tumors and there was 10 ml. of blood-tinged ascitic fluid. There was a large tumor of the omentum, composed of nodules which had fused. The genital fat was almost completely replaced by tumors. There were numerous tumors throughout the mesentery. The liver was studded with small implants and one lobe of the liver was obliterated. The tumor on the diaphragm had penetrated and was growing in the thoracic cavity. There were many implants on the peritoneal

wall (not shown) and on the kidney. This illustrates the extensive involvement commonly observed when transfers are made by intraperitoneal inoculation of a suspension of tissue cells.

Effect of the Amount of Tissue Transferred Upon the Success of Transfer

Although most of the transfers were made with 100 mg. of tissue, adopted as standard procedure, smaller amounts have been transferred successfully. The effect of the amount of tissue transferred upon the success of the transfer is shown in Table V. These are the same data as appear in Table I. Four hundred and thirty-six rats received transfers of 100 mg. of tissue and 237 received tissue in the amounts of 0.5, 0.8, 1, 2, 5, 10, 25, 40, and 50 mg. When differing amounts of tissue were used, the percentage of "takes" varied between 61.1 and 100. Hosts receiving 5 mg. of tissue or less showed 74.2 per cent of "takes," those with 10 to 40 mg., 65.9 per cent, and those with either 50 or 100 mg., 81.0 per cent. The entire group receiving 40 mg. or less showed a lower percentage of "takes" than the groups with 50 and 100 mg., but there seem to be no trends within that former group.

TABLE V. EFFECT OF AMOUNT OF TISSUE TRANSFERRED UPON THE SUCCESS OF TRANSFER

TRANSFERS		HOSTS		
AMOUNT OF TUMOR (MG.)	NO. OF TISSUES	NO.	NO. POSITIVE	% POSITIVE
0.5	9	16	11	68.8
0.8	1	5	5	100.0
1	9	22	14	63.6
2	2	6	5	83.3
5	7	17	14	82.4
10	13	36	22	61.1
20	10	33	21	63.6
25	8	19	14	73.7
30	1	2	2	100.0
40	10	39	26	66.7
50	4	42	34	81.0
100	137	436	353	81.0

Increase in the Transplantability of the Tumor

If these data presented above are summarized, using only transfers in which three hosts were used for each tissue, 93 groups of males and 28 groups of females are obtained. The male hosts have been divided into three chronological groups of 31 groups of three hosts each. In the earliest group (Group I) 10 of the 31 groups (32.3 per cent) showed all three of the transfers successful in each group, in the intermediate group (Group II) 51.6 per cent, and in the last group (Group III) 74.2 per cent. In the remaining groups some transfers in each group of three were negative. The percentage of successful "takes" for Group I was 72 (67 of 93 transfers), for Group II, 79.6 (74 of 93 transfers), and for Group III, 90.3 (84 of 93 transfers). These data seem to indicate an increase in the ease of transplantability with repeated transfer of the tumor. During the entire period 49 (52.7 per cent) of the 93 groups showed three successful transfers in each group of three hosts, and 225 (80.6 per cent) of the 279 transfers were successful. During the same period 28 groups of three females each received transfers of tumor tissue. Seventeen (60.7 per cent) of the 28 groups of three showed all three transfers of each group successful, and 67 (79.8 per cent) of the 84 transfers. The males received transfers from 92 tissues and the females from 28 tissues, usually the same tissues as received by the male hosts. These data appear in Table VI.

TABLE VI. INCREASE IN THE TRANSPLANTABILITY OF THE TUMOR

HOSTS	NO. OF TISSUES	NO. OF HOSTS	NO. OF GROUPS OF 3	GROUPS ALL POSITIVE		GROUPS POSITIVE AND NEGATIVE		TOTAL TRANSFERS	
				NO.	%	NO.	%	NO. POSITIVE	% POSITIVE
Male Hosts									
Group I	30	93	31	10	32.3	21	67.7	67	72.0
Group II	31	93	31	16	51.6	15	48.4	74	79.6
Group III	31	93	31	23	74.2	8	25.8	84	90.3
Total	92	279	93	49	52.7	44	47.3	225	80.6
Female Hosts	28	84	28	17	60.7	11	39.3	67	79.8

Course of the Tumor Development

In order to study the mode of transmission and the rate of growth of the transplanted tumors, transfers have been made to a group of rats and four or five rats have been sacrificed at various time intervals. Three such groups were inoculated for this purpose.

Experiment 1.—Four groups of five male rats weighing 205 ± 5 grams were used as hosts. Each host received an intraperitoneal inoculation of 2 ml. of a suspension of tumor tissue equivalent to 100 mg. of tumor. The tumor used was characteristic soft friable tissue from an omental tumor of the thirteenth generation obtained 103 days after inoculation.

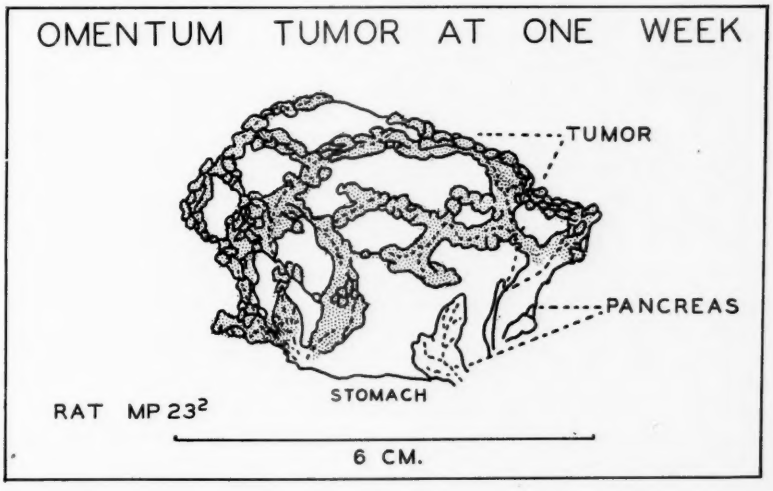

Fig. 6.—Drawing of an omental tumor in Rat MP 23² seven days after intraperitoneal transfer of a suspension of tumor tissue. Shaded areas show early tumor and the plain areas the connecting membrane of the omentum.

Development at 7 days: Five rats were sacrificed on the seventh day after inoculation. All showed definite tumor development in the omentum in the form of small nodules which followed the blood supply, giving the tissue a lacelike appearance. This is illustrated by the drawing of Rat MP 23² (Fig. 6). The omental tumor measured 4 by 6 cm. and was composed of 1 to 3 mm. nodules along the blood vessels, held together by the very thin sac of the omentum. The nodules were firm pale tissue. There was also a tumor in the genital fat. The omental tumor of Rat MP 24² was less extensive than that of Rat MP 23² but there was a 5 mm. tumor over the xiphoid process which was of a more advanced stage and was hemorrhagic. The omental tumor of Rat MP 25² was similar to but showed fewer nodules than Rat MP 23²; there was a 5 mm. tumor in the genital fat; the membrane over the caudate lobe of the liver had several beginning tumors. The omental tumor of Rat MP 26² differed from that of Rat MP 23² in that the nodules com-

prising it were larger and firmer and the growth extended to the membrane surrounding the spleen and adjoining the stomach. A tumor was present in the mesentery. In Rat MP 27[2] the omental tumor was similar to Rat MP 23[2] but the membrane surrounding the caudate lobe of the liver was extensively involved. There was no evidence of an inflammatory process in any of these rats.

Development at 14 days: In the group of five rats sacrificed at the end of 14 days, two were negative. The tumors of the other three were similar to those of the previous week but showed more advanced development and a small amount of ascitic fluid. In Rat MP 28[2] the omental tumor was composed of nodules 1 to 5 mm. in diameter, and the larger nodules were soft friable pink tissue. Small tumors were found surrounding the spleen, on the spleen, in the genital fat, and at the injection site. The omental tumor of Rat MP 37[2] was less extensive and was composed of flat nodules; there was a 2 mm. tumor on the caudate lobe of the liver. Rat MP 38[2] showed rapid tumor growth. The firm nodules of the omental tumor were 1 to 8 mm. in diameter and gave a nodular rather than lacelike appearance to the tumor. The tumor growing around the spleen was advanced, consisting of soft hemorrhagic tumor tissue. There were peritoneal implants, implants on the liver, and two approximately 5 mm. tumors in the mesentery. The omental tumor was transferred to three male rats (approximately 260 grams). In spite of the relatively early development of the tumor, 100 mg. of the tissue produced extensive tumors in the hosts and they reached a terminal stage in 23, 28, and 41 days, respectively. They were distended with 64, 48, and 100 ml. of ascitic fluid, respectively. Extensive tumor formation was found in the omentum, mesentery, genital fat, liver site, peritoneal wall, and the diaphragm.

Development at 21 days: The five hosts sacrificed at 21 days after inoculation showed advanced and extensive tumor development, as illustrated by Rat MP 56[2] in Fig. 7. When the tumors were exposed, they were similar to those appearing in Rat MP 67 sacrificed at 21 days (See Fig. 5). A characteristic finding was a large quantity of ascitic fluid. Rat MP 56[2] had 37 ml. of ascitic fluid. The omental tumor measured 1 by 4.5 by 8 cm. and was composed of nodules 5 to 8 mm. in diameter. The omental membrane was not visible on the outside of the tumor. However, the tumor retained the sac formation. There were tumors under the liver and the caudate lobe was obliterated. There were many 5 mm. tumors in the genital fat and some in the mesentery. Rat MP 45[2] had an omental tumor similar to that of Rat MP 56[2] which measured 2 by 4.5 by 7.5 cm. and was comprised of nodules 5 to 10 mm. in diameter. The caudate lobe of the liver was replaced by tumor and the tumor growing under the liver measured 1 by 2 by 3 cm. The mesentery contained many 5 mm. tumors and the genital fat several. There was a 1 by 1 by 1.5 cm. implant at the injection site and the peritoneal wall was studded with small implants. There were 40 ml. of ascitic fluid. The tumor growth in Rat MP 46[2] was slight and there was no ascitic fluid. There were 5 mm. tumors in the omentum, beneath the caudate lobe of the liver, in the genital fat, and at the injection site. Rat MP 47[2] showed nothing striking. There were 28 ml. of ascitic fluid. The omental tumor was of typically nodular, soft, and hemorrhagic tissue, measured 1 by 3.5 by 4.5 cm., and was comprised of 5 to 15 mm. nodules. The caudate lobe of the liver was replaced by a tumor measuring 0.5 by 1.5 by 2.5 cm. There were implants and tumors in the genital fat. Rat MP 48[2] showed earlier development of the omental tumor but the nodules were composed of soft friable tissue and were 5 to 10 mm. in size. A more advanced hemorrhagic tumor, measuring 0.5 by 1 by 2.5 cm., was found beneath the spleen. The caudate lobe of the liver was almost completely replaced by tumor. There was a tumor in the genital fat and an implant at the injection site.

Development at 28 days: Of the five hosts sacrificed at 28 days, three were negative and no particular advancement was shown by the others. Rat MP 58[2] had an encapsulated tumor arising in the omentum which was attached to the genital fat. It measured 1 by 2 by 3 cm. At one point the capsule had ruptured and characteristic soft hemorrhagic tissue was being extruded. Tumors were growing in the membrane surrounding the caudate lobe and spleen. There were 6 ml. of ascitic fluid. Rat MP 78[2] had 15 ml. of ascitic fluid. The omental tumor was not extensive but was also attached to the genital fat. Two tumors approximately 2 cm. in diameter were growing under the liver. There were implants. The tumors in MP 123[2] were 5 to 15 mm. in diameter and were found in the omentum, mesentery, in the liver site, and on the peritoneum.

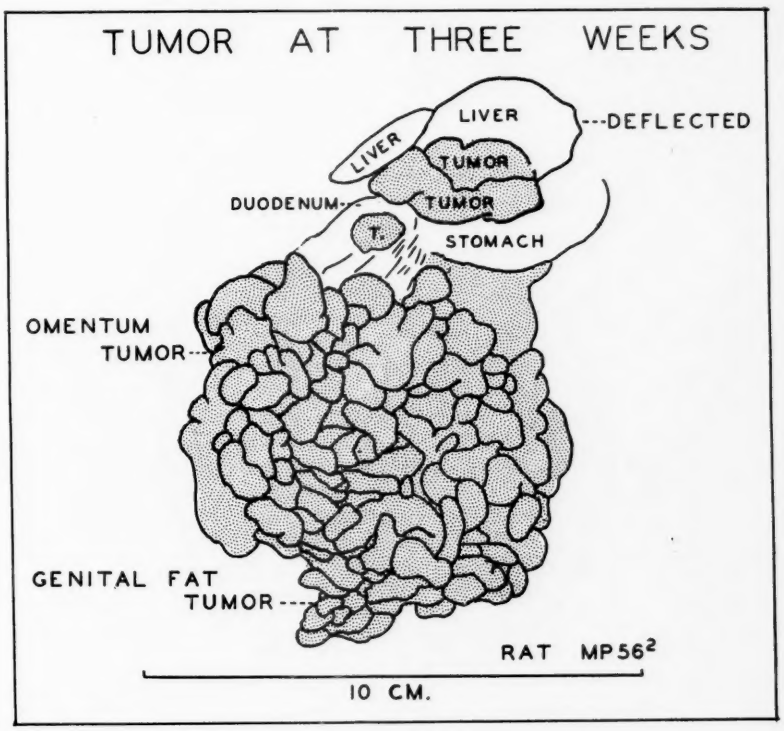

Fig. 7.—Drawing of Rat MP 56[2] twenty-one days after intraperitoneal transfer of a suspension of tumor tissue. Same experimental group as illustrated in Fig. 6.

Experiment 2.—This experiment was carried out to confirm the findings of Experiment 1. One hundred milligrams of a mesentery tumor in suspension were inoculated into 23 male rats weighing 205 to 260 grams. The tumor was of the fourteenth generation and was obtained 51 days after transfer. Groups of these hosts were sacrificed at 1, 2, 3, and 4 weeks and in general they confirm the findings of the previous experiment.

Development at 7 days: The five rats sacrificed at 7 days after inoculation resembled those of Experiment 1 and showed no deviations from the findings illustrated by Fig. 6. Tumors of the omentum, liver site, mesentery, and implants were found also.

Development at 14 days: In the group of five hosts sacrificed at 14 days, two showed no evidence of tumor formation except several tiny nodules. The other three showed more advanced development of the omental tumor than at the same period in Experiment 1. The omental tumor measured 5 cm. in each and was composed of tumor nodules which were firmer and more hemorrhagic. One omental tumor was encapsulated by a thin shiny membrane but on the inside the tumor was the usual friable tissue. Tumors were found in the liver site and on the

peritoneal wall but no tumors were present in the genital fat or in the mesentery.

Development at 21 days: Of the original group of five hosts to be sacrificed at 21 days, one was sacrificed at 18 days because of the terminal condition. A cystic and necrotic tumor was found growing on the posterior abdominal wall and obstructing the colon and bladder. The omental tumor measured 3.5 by 4 cm. and was comprised of nodules 5 to 15 mm. in size. Tumors were also found in the region of the caudate lobe of the liver, in the mesentery and genital fat, and on the peritoneum. At 21 days five hosts were sacrificed. All of these showed well-advanced but less extensively developed omental tumors than Rat MP 56[2], Fig. 7. Tumors were found also in the region of the liver, the genital fat, mesentery, and on the peritoneum. A third rat showed about a two-week development of the omental tumor, measuring 4.5 by 5 cm., and comprised of 5 mm. nodules. Other tumors were found in the genital fat, liver site, and peritoneum. A fourth rat showed advanced development with an omental tumor 1 by 4 by 5 cm., which was partly encapsulated. This had ruptured in several areas and characteristic friable tissue was being extruded. Other tumors were found in the mesentery, liver site, genital fat, peritoneum, and diaphragm. The fifth rat was in a terminal stage with very advanced tumors in all of the usual sites. The omental tumor measured 1 by 5 by 5 cm. and was composed of nodules 5 to 15 mm. in diameter and of varying degrees of tumor development. The tumor extended under the stomach and spleen and liver and entirely surrounded the caudate lobe. The genital fat was completely replaced by tumor. The peritoneum was studded with small implants, and tumors were found in the mesentery. The tumor growing on the diaphragm had perforated it and was extending into the thoracic cavity.

Development at 28 days: Of the five rats to have been autopsied at 28 days, one died on the eighteenth day and one was sacrificed on the twenty-sixth day after inoculation. The rat that died on the eighteenth day had an omental tumor, 2 by 4 by 5 cm., which was composed of hemorrhagic tumor tissue. There were numerous implants and tumors in the mesentery, genital fat, and liver site. The other host had an encapsulated omental tumor measuring 1 by 3 by 7 cm.; the tissue was typical. This tumor was connected to a 1.5 cm. tumor in the mesentery, to genital fat tumors, and to an extensive liver site tumor measuring 2 by 3.5 by 3.5 cm. which was growing on the median lobe and embedded in the caudate lobe. The third rat had been used to complete the group sacrificed at 21 days. A fourth host had one encapsulated tumor (3 by 3.5 cm.) surrounding the cecum and another the colon. These were attached to the omentum which contained only a few tumor nodules. There were small tumors in all the usual sites. Three rats showed only scattered small tumors and nothing unusual.

Experiment 3.—This experiment was designed to compare the manner of the tumor development in female hosts. Four groups of four female rats each (165 to 185 grams) were inoculated intraperitoneally with a suspension of 100 mg. of tumor. The tumor was growing between the lobes of the liver and was obtained 31 days after transfer. It was in the tenth generation. These findings were similar to those of Experiments 1 and 2 except possibly that the tumors developed more rapidly.

Development at 7 days: The four hosts sacrificed at 7 days showed early omental tumors similar to those described in the previous experiments and illustrated by Fig. 6. Tumors were found in the other usual sites.

Development at 14 days: Four rats were sacrificed 14 days after inoculation. In one host the omental tumor (1 by 4 by 4.5 cm.) was more advanced than those found in Experiments 1 and 2 and there were numerous tumors and implants in all the usual sites. In two others the tumors were much more advanced. In one rat the omental tumor measured 1 by 4.5 by 4.5 cm. and in the other 1 by 5 by 7 cm. In

the latter the caudate lobe was embedded in a tumor measuring 1 by 2 by 2.5 cm. Other tumors were found in both hosts. The fourth rat showed only a few tumors.

Development at 21 days: In three of the four rats sacrificed at 21 days no particular findings were noted other than tumors in the usual sites which ranged in size to 1 by 1 by 2 cm. The fourth rat had extensive tumor growth and 69 ml. of ascitic fluid. The omental tumor was 1 by 4.5 by 6.5 cm. and was an advanced tumor. Numerous other tumors were found. One hundred milligrams of the omental tumor were transferred to three young male hosts. They were sacrificed at 19, 28, and 38 days because of extensive tumor growth.

Development at 28 days: Only one of the four rats survived 28 days. In this rat only small tumors were found and none in the omentum or liver site. One host died at 18 days with an omental tumor, 1 by 4 by 6 cm., and numerous tumors in all the other sites. A second rat died at 21 days and showed an omental tumor, 1 by 4 by 5.5 cm., a liver site tumor, 1 by 2.5 by 4 cm., and tumors in all the usual sites. The third rat died at 27 days and showed an omental tumor, 2 by 3.5 by 5.5 cm., a liver site tumor, 1 by 2 by 2 cm., and genital fat tumors. These three hosts had 19, 17, and 41 ml. of ascitic fluid, respectively.

Ovaries and Estrus Cycles of Tumor Hosts

In many instances at autopsy of the tumor hosts the ovaries appeared abnormal. They were small and yellow and composed chiefly of corpora lutea. It seemed of interest to make microscopic examinations of these ovaries and also those showing other abnormalities. Seventy-three ovaries from 44 tumor-bearing rats were examined. In general, the changes observed were not striking but several instances of tumorlike changes were observed. In ovaries which were essentially normal there was a tendency toward luteinization and an absence of follicles and interstitial tissue. In ovaries in which follicles were present there was a tendency toward irregular arrangement of the granulosa cells. Since the tumor resembles ovarian stroma cells, it was difficult to distinguish minor changes. In several instances tumorlike development appeared to arise from old corpora lutea. In two rats small spherical tumors arose from ovarian tissue in the region of the hilum. Although the genital fat was the site of extensive tumor formation and the ovary was often completely encapsulated by tumor, in general the tumor did not invade the ovary itself. Twenty ovaries were transferred, usually by the tissue implantation technique, but there were no successful transfers of tumor tissue.

In one host (FP 125) both ovaries were replaced by smooth bright yellow spherical masses. The right weighed 26 mg. and the left, 58.4 mg. The latter had a small corpus luteum on the surface. The tissue was firm and translucent and was similar to a young tumor. Microscopically the tissue resembled the tumor of the host but there were other cell types present also. One tumor seemed to have arisen from an old corpus luteum but in general ovarian structures were absent. Sixteen and eight-tenths milligrams of the left tumor were inoculated but failed to "take." The cycle predominated in the estrus phase.

The changes in the ovaries were less marked than those found in a series of transfers from the tumor of the ovariectomized rat FP 0456[4] mentioned briefly above. In the second generation of this tumor all four female hosts showed marked ovarian pathology. In one host both ovaries contained abnormally large and degenerate corpora lutea and one ovary measured 3 by 3 by 5 mm. The second rat had one relatively

normal ovary but it was attached to the tumor in which it was embedded. The other ovary had been completely replaced by a solid ovarian tumor approximately 5 mm. in diameter. This tumor was pale yellow translucent tissue resembling a fibroma. Microscopically some of the tissue resembled the other tumors of the host but these areas were interspersed with fibrous tissue and tissue of other cell types. In the third rat one ovary was normal but the other had been replaced by a 10 mm. tumor. This tumor was composed of firm fibrous tissue with corpora lutea scattered throughout. On microscopic examination the corpora lutea appeared to have been invaded almost completely by tumor tissue. In the fourth rat one ovary was grossly normal but the other had a 3 by 6 mm. tumor arising from it. The ovarian tissue was old corpora lutea. Although the tumor retained some of the contours of the old corpora lutea as though they had been invaded and enlarged by the tumor no other ovarian tissue was observed.

Because of the ovarian changes, estrus cycles were followed in a group of rats beginning either prior to the transfer of the tumor or on the day of transfer and continuing to the terminal stages. When the estrus cycles were plotted graphically, ten showed a tendency toward an estrus phase, one to diestrus, and thirty to normal cycles. This incidence of a tendency toward the estrus phase may be somewhat higher than normal. The estrus smears were not similar to those obtained when cornification appears from routine vaginal smearing. Of the 41 of these rats that developed tumors, microscopic examinations were made of the ovaries of 16. There were no significant findings in the correlation of the estrus cycles with the microscopic findings in the ovaries.

Pregnancy and Tumor Development

Several attempts were made to test the effect of the tumor upon fertility and on the course of pregnancy.

Six females of known fertility were inoculated intraperitoneally with 50 mg. of tumor tissue. After 23 days they were to be mated with six males of known fertility. Two of the female hosts died from extensive tumor development at the end of three weeks and before mating. Two failed to become pregnant; one of these died from the tumor on the thirty-second day after inoculation; the other was negative after 59 days. One host did not show tumor growth at the time she delivered a small normal litter but at 102 days died with extensive tumor formation including an omental tumor, 2.5 by 4 by 5.5 cm. The sixth rat died from the tumor on the eleventh day of pregnancy and the thirty-fifth day after inoculation. Autopsy revealed seven macerated fetuses.

Five males of proved fertility received 50 mg. of a suspension tumor intraperitoneally 23 days prior to mating. One rat died on the twenty-first day, one on the twenty-third day, one on the twenty-eighth, and one on the thirty-sixth day and before adequate tests could be made. Only one of the nine females became pregnant. The fifth host survived 84 days and four of the eight females mated with this host had normal litters.

Five pregnant rats with histories of two to four normal pregnancies were inoculated intraperitoneally with 50 mg. of tumor tissue on the twelfth day of pregnancy. One died four days after inoculation; of the three that developed extensive tumors, two failed to go to term and one delivered a litter of four at term; the fifth host delivered a litter of three at term but autopsy revealed only one 1 cm. tumor in the omentum.

Another pregnant rat with a known pregnancy history was inoculated on the thirteenth day of pregnancy. A litter of six slightly undersized young was born at term. The young survived in spite of the inadequate care the mother was able to give. The mother died 32 days after inoculation and 23 days after delivery. At autopsy 92 ml. of ascitic fluid were removed from the abdominal cavity and characteristic exten-

sive tumor growth was observed. Tumors were found throughout the abdominal cavity, in the mesentery, on the diaphragm, genital fat, under the liver, and included a tumor of the omentum measuring 1 by 2 by 4 cm., a tumor under the liver measuring 2 by 2 by 3 cm., and a mesentery tumor 1 by 2 by 3 cm.

In general, these preliminary experiments show little evidence that either the course of pregnancy or the tumor growth influenced the other co-exsting condition except possibly to have a deleterious effect upon pregnancy.

Summary

A transplantable rat sarcoma arising in a colony of ovariectomized rats used for the assay of estrogens has been investigated. The tumor was transmitted by transfer of tissue fragments or by inoculation of a suspension of tissue. Bacteriologic examinations were negative and the tumor was not transmitted by filtrates of tumor tissue.

The tumor was carried on in eleven lines: three lines for 10 generations, one each for 12, 17, and 19 generations, two each for 21 and 22, and one for 24. No line died out spontaneously. No tumors regressed.

The tumor remained characteristic regardless of the site of transfer and did not change type at any time. The transplantability increased with repeated transfer.

Of the 1,171 transfers made by intraperitoneal inoculation, 839 (71.7 per cent) were successful irrespective of the amount of tissue transferred. In a group of 436 hosts which received 100 mg. of tumor tissue, 353 hosts (81.0 per cent) developed tumors. Eighty and eight-tenths per cent of the male hosts (257 of the 318 hosts) showed successful transfers and 81.4 per cent of the female hosts (96 of the 118 hosts), indicating no sex difference in the susceptibility of the hosts to the tumor.

In a group of 383 hosts which received 100 mg. of tumor tissue, 318 (83 per cent) were successful. Of these, 43 hosts (13.5 per cent) survived less than 20 days, 136 hosts (35.5 per cent) survived 20 to 29 days, and 139 hosts (36.3 per cent) survived longer than 30 days.

The sites of the tumor development in a group of 179 hosts receiving 100 mg. of tumor tissue intraperitoneally and surviving less than 30 days were: omentum 176, liver and adjacent tissues 171, genital fat 156, implants 198, mesentery 149, diaphragm 91, subcutaneous 53, intestinal tract 23, kidney and adjacent tissues 14, spleen 4, thoracic cavity 3, and stomach 1. Other sites of tumor formation observed were the ovary, testis, seminal vesicle, thymus, lymph nodes, heart, and lung. Ascitic fluid accompanied advanced tumors. The greatest number of sites of tumor formation in one host was ten. Forty-seven of the 179 hosts (26.3 per cent) showed tumors in seven sites. One hundred and fifty-six hosts (87.1 per cent) had tumors in four to eight sites.

Amounts of tumor tissue from 0.5 to 100 mg. were transferred. The group of hosts receiving 40 mg. or less showed a slightly lower percentage of "takes" than those receiving 50 or 100 mg. of tissue.

The transplantability of the tumor increased with repeated transfers. Three chronological groups of male hosts composed of 31 groups of three hosts each received transfers from 92 tumors. The earliest group showed 72 per cent successful transfers, the second group 79.6 per cent and the latest group 90.3 per cent.

Three experiments were carried out to determine the mode of transmission and the rate of development of the transfers. A large group of hosts was inoculated and small groups were sacrificed at weekly intervals. Tumor development at the various intervals is described. Tumors were observed at seven days.

The effect of tumor growth on the estrus cycle and upon the ovaries has been investigated.

Several experiments were undertaken to determine the effect of the tumor upon fertility and the course of pregnancy, and of pregnancy upon the tumor development.

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CESAREAN SECTION MORTALITY*

WILLIAM J. DIECKMANN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago, and the Chicago Lying-in Hospital)

THE maternal mortality from cesarean section in the United States, according to a review published in 1941, by Gordon and Rosenthal, is probably "at least 10 per cent and possibly approaches 15 per cent." Such a high mortality seems improbable, but various reports since 1930, still give mortalities for cesarean section of 0 to 17 per cent. Earlier reports give figures which are even higher for some small hospitals. Furthermore, studies of maternal deaths reveal that cesarean section had been performed in 24 per cent of the deaths in the Fifteen State Study, in 20 per cent of the New York City deaths, in 14 per cent of the Philadelphia deaths and in 20 per cent of the Chicago deaths. Five United States maternity hospitals staffed by trained obstetricians have performed 6,335 cesarean sections since 1931, with an *uncorrected* average maternal mortality of 1.46 per cent, range from 0.61 to 3.1 per cent. The reduction of the cesarean mortality in Philadelphia from 6.1 to 1.3 per cent, the report by DeNormandie of 11,030 operations in Massachusetts with a mortality of 2.46 per cent, and our own results indicate that cesarean section can be performed with a mortality of 1 to 2 per cent in general hospitals and a mortality of 0.5 to 1 per cent in maternity hospitals.

Phaneuf, in 1943, stated in a discussion that the maternal mortality from cesarean section of 1.96 per cent at the Philadelphia Lying-in

*Presented at a meeting of the Chicago Gynecological Society, Nov. 17, 1944.

Hospital was not excessive. He also stated that many of the deaths after cesarean section are attributed to the operation instead of to the existing pathology (placenta previa, abruptio placenta, contracted pelvis, toxemia, etc.). Unfortunately, a compilation Table I, of 1,922 cesarean deaths reveals that 38 per cent of the deaths were due to sepsis, 30 per cent to shock and hemorrhage and 19 per cent to toxemia, a total of 87 per cent. Certainly one-half and possibly two-thirds of these deaths are preventable.

TABLE I. AUTOPSY FINDINGS IN 1922 CESAREAN SECTIONS

CAUSE OF DEATH	RANGE %	AVERAGE %
Peritonitis, septicemia, ileus, intestinal obstruction	27 to 50	38
Pulmonary embolism	0 to 11	7
Shock and hemorrhage—total	21 to 36	30
Placenta previa	0 to 9	5
Abruptio placenta	0 to 7	6
Heart failure	0 to 9	5
Eclampsia, toxemia, vascular-renal disease, pulmonary edema	8 to 37	19
Lobar pneumonia	0 to 14	3
Anesthesia—aspiration pneumonia	0 to 12	3
Spinal anesthesia		(3)
Incompatible blood transfusion		(2)
Tuberculosis		(1)

( ) = Based on small number.

Plass reported that in Iowa, 29 per cent of the cesarean section deaths occurred on the first day, and 22 per cent on the second and third postoperative days. Obviously, almost 51 per cent of the deaths were from shock and hemorrhage or overwhelming infection. We are responsible for any puerperal infection, even in elective operations, until evidence is presented to the contrary. Blood transfusions will prevent death from hemorrhage.

Beck states: "The general idea that most of us hold is that the mortality from cesarean section ought not to be over 1 per cent, if the right operation is done on the right patient at the right time. We pay too much attention to indications and too little attention to contraindications."

Irving believes that when cesarean mortality in large clinics over a period of years is less than 1 per cent, then it will be time to broaden the indications. Schumann believes that cesarean section in skilled hands has a maternal mortality so low as to be practically negligible. Data in a subsequent table do not confirm Schumann's belief. There is an inevitable difference in the mortality between private and clinic patients. The clinic patient may not have seen a doctor, or there may have been errors in judgment made by the resident staff. Thus, there was only one cesarean section death (tuberculous meningitis) in our private patients who comprise 40 per cent of our service.

Kennedy, discussing cesarean section, has stated "to place a scar in the uterus and abdomen of a young woman during her first childbirth is to suspend a guillotine over her neck for the rest of her life. Where will she be during her next labor; will she fall in the hands of an accomplished surgeon, or will she die from a ruptured uterine scar?" These remarks are pertinent, but a cesarean section performed at the proper time for a proper indication will ensure a live mother and baby. I have seen death too from vaginal delivery as well as

extensive lacerations which prevented future pregnancies and/or caused dyspareunia and marital difficulties, at times ending in divorce. Subsequent vaginal plastic surgery is not always successful and is not without mortality.

DeLee always used the term "watchful expectancy" in cases of prolonged labor. Hunt, one of our former residents, transposed this term to "hopeful procrastination." We would hope that the cervix would dilate and hope that the head would engage, but what if they did not, and how long could we hope. None of us are infallible in our judgment, but nothing arouses me more than to be called as a consultant and find: 1. patient with a borderline pelvis, ruptured membranes for 48 hours or longer, repeated attempts at medical induction of labor and many rectal examinations; or 2. patient with severe pre-eclampsia at 37 weeks, repeated attempts at medical induction of labor, and many rectal examinations. In both patients *only a vaginal examination* made early could have revealed whether or not labor would begin within 12, 24, or X hours in the first case, and if medical induction had any chance of success in the second.

Mellor's statement "Watchful waiting is an essential virtue in obstetric management, but look out for criminal procrastination just around the corner," is pointed. Book knowledge of obstetrics is necessary, but only the experience gained in clinical obstetrics will enable the doctor to decide which is "watchful expectancy," which is "hopeful procrastination" and which is "*criminal negligence.*"

TABLE II. CESAREAN MATERNAL MORTALITY—PER CENT

	CONTRACTED PELVIS			
	ROUTH 1911	HOLLAND 1921	BROOKLYN 1928	
	CLASSICAL M.M. %	CERVICAL M.M. %	CLASSICAL M.M. %	CERVICAL M.M. %
Not in labor	3.6	1.6	3.5	0.0
Early labor		1.8	6.4*	
In labor, membranes intact	2.2			
In labor, 6 to 24 hours			7.1	0.0
In labor, 24 to 72 hours		10.0	9.1	5.7
In labor, membranes ruptured	11.4			
Frequent examinations or attempts at delivery	37.9	27.0	13.6	
After induction of labor		14.0		
No vaginal examinations, all cases—2 + days of labor			5.9	1.5
Vaginal examinations, all cases—2 + days of labor			13.5	10.5
Total mortality %:	9.4	4.2	5.9	4.3

*Labor up to 6 hours.

Routh's data for the period 1891 to 1910, given in Table II demonstrate the mortality of cesarean section after prolonged rupture of the membranes, frequent examinations or attempts at delivery. The mortality in elective cesarean section was almost as low then as it is now in many hospitals. The next comprehensive report by Holland in 1921, and the Brooklyn report in 1928, show similar data, demonstrating the high mortality after prolonged labor or vaginal manipulations. It seems unbelievable that the dangers so clearly illustrated in these three studies are still not appreciated by many obstetricians.

Consultation experience and common sense dictate that you must give the doctor some positive advice besides the "don't." A cesarean section in cephalopelvic disproportion while the patient is still not infected;

in the severe pre-eclamptic patient before convulsions have occurred; or in the patient with severe eclampsia (after 8 to 12 hours medical treatment), while the patient is still a good operative risk, is far better treatment than insistence upon vaginal delivery at any cost. Deaths do occur after vaginal delivery, but many doctors attribute them to an act of God. Each patient must be individualized, and the proper type of delivery selected for her particular complication. The obstetrician should not apologize for performing an indicated cesarean section, but he should be censured if he kills mother or baby by selecting the wrong type of delivery, whether it be by vaginal or abdominal route.

Monthly meetings in some cities by a committee of competent obstetricians, at which each maternal death is discussed, have resulted in a marked decrease in the number of deaths. Philadelphia in 1931, had 601 cesarean sections (incidence of 1.8 per cent) with 38 deaths (6.1 per cent) and in 1932, 591 operations (1.8 per cent) with 36 deaths (6.0 per cent). In 1939, there were 857 cesareans (2.8 per cent) with 11 deaths (1.3 per cent), and in 1942, 1,222 operations (2.8 per cent) with 29 deaths (2.4 per cent).

Cesarean section with survival of the patient, after several unsuccessful attempts to "break up" a breech (40 hours of labor); after "failed forceps and failed version" (two different doctors tried each) and cesarean section for a hydrocephalic head that was free in the uterine cavity; is the result of chance and is not due to good judgment or operative skill. I have repeatedly been told of such cases by general surgeons who thought that their treatment had been right because the patient survived and by obstetricians who were honest enough to admit their mistake. Realization of the possibility of death from sepsis has prompted many obstetricians to an earlier use of cesarean section while the patient is still "clean." This has caused some increase in the incidence, but an absolute decrease in the maternal mortality.

Cesarean section means the abdominal delivery of the fetus. Skeel limited the term to fetuses of more than 30 weeks' gestation or weighing at least 1,500 grams. Adair included fetuses of more than 22 weeks or weighing at least 400 grams. Eastman, Stander, Irving and Cosgrove have used Skeel's criteria. Our cesarean sections were classified according to Adair's criteria up to 1943. However, the total number of fetuses weighing less than 1,500 was only 3 per cent in 419 abdominal deliveries. There is less danger from lochiometra and peritonitis if the fetus weighs less than 1,500 grams and also much less morbidity.

I have listed in Table III, the maternal mortality for cesarean section for large series of patients from 1891 up to the present time. Laparotomies for rupture of the uterus are not included. It is disappointing to note that the average mortality is still very high. However, the results achieved in the maternity hospitals, in Massachusetts, in Philadelphia, etc., demonstrate that marked improvement has occurred in evaluating the dangers of the operation.

Winter received information from 384 operators concerning 4,450 cesarean sections performed in Germany during 1928; 316 or 7.1 per cent died. Winter divided the mortality into three groups: 1. mortality due to indications for which the operation was performed, 120

TABLE III. HOSPITAL STATISTICS

HOSPITAL	YEARS	DELIVERIES 1,500 GM. +	TOTAL MATERNAL MORTALITY %	CESAREAN SECTION			
				NUMBER	INCIDENCE %	MORTALITY MATERNAL	– % FETAL
Routh—Collective	1891 to 1895			83		28.00	
Routh—Collective	1906 to 1910			711		8.10	
Holland—Collective	1911 to 1920			4,197		7.20	12.0
Bannister—Coll. 5 Brit. Mat.	1928			1,763		5.80	
Winters—Coll. Germany	1928			4,450		7.10	9.0
Brooklyn, N. Y.—Collective	1921 to 1926			1,805		7.00	8.5
New Orleans—Coll. Gyn. Soc.	1921 to 1926	16,323		300	1.80	16.10	18.9
New Orleans—Coll. King	1927 to 1936	52,629		1,108	2.08	5.90	10.8
Philadelphia—Coll. Lull	1931	23,511		573	2.43	6.80	12.8
Philadelphia—Coll. Lull	1941	30,939		594	2.88	2.46	3.3
Chicago	1940 and 1941			2,500–	2.40	2.40	
Irving—Collective	1937			7,174		2.15	9.1
Arnold—Collective	1931 to 1939			15,768		4.69	8.8
Massachusetts, DeNormandie	1937 to 1942	272,752		11,030	3.30	2.46	
Chicago Lying-in	1931 to 1944	*39,709[a]	0.150	1,790[a]	4.74	0.61	8.7[a]
Chicago Lying-in	1942 to 1944	7,394[b]	0.080	317[b]	4.28	0.00	4.4[b]
Boston Lying-in	1931 to 1936	*20,364	0.250	584	2.86	3.10	8.8
Boston Lying-in	1942 and 1943	* 9,632	0.160	225	2.34	0.00	6.5
New York Lying-in	1932 to 1939	*27,125	0.240	577	2.13	1.73	
Philadelphia Lying-in	1932 to 1942	*22,754	0.400	1,322	5.80	1.98	8.2
Margaret Hague	1932 to 1943	*68,786	0.290	1,837	2.67	1.52	
	*Total	188,370	0.244	6,335	3.36	1.46	
Rotunda—Ireland	1938 to 1940	6,414	0.430	104	1.62	4.00	6.0
Glasgow Royal Mat.	1940	3,032	1.500	206	6.70	1.00	
Edinburgh Royal Mat.	1938	2,058	1.500	77	3.70	1.30	8.1
Queen Charlotte	1942	2,312	0.430	21	0.91	0.00	9.5
Women's Hosp., Melbourne	1920 to 1935	43,727			0.80	6.00	

[a] = Fetus weighed 400 Gm. or more.
[b] = Fetus weighed 1500 Gm. or more.
Coll. = Collective.
*For total.

TABLE IV. CESAREAN SECTIONS PERFORMED BY ONE OPERATOR

		NUMBER	MORTALITY %	
			MATERNAL	FETAL
Schumann	1939	120	0.00	2.5
Phaneuf	1934	575	4.20	5.9
Phaneuf—Consecutive low cervical		292	2.30	
Marshall	1939	246	0.00	5.7
Gustafson	1931 to 1943	208	0.96	3.3
Davis	1931 to 1944	450+	(3)	
Dieckmann	1931 to 1944	375+	(1)	
Hesseltine	1931 to 1944	250+	(2)	

( ) = Number of patients who died.

TABLE V. CESAREAN SECTION DEATHS OF CHICAGO LYING-IN HOSPITAL (1931 TO 1944)*

PATIENT	INDICATION	LIVED	TYPE OPERATION	CAUSE OF DEATH
1. As.	Tuberculous meningitis	11 days	Lap. Trach.	(A) Tuberculous meningitis
2. Gr.	Tuberculous meningitis	4 hours	Classic	Tuberculous meningitis
3. Se.	Contracted pelvis	25 hours	Classic	(A) Abdominal hemorrhage
4. An.	Myoma	9 days	Classic and Myomectomy	(A) Peritonitis
5. Da.	Placenta previa	3 hours	Lap. Trach.	(A) Exsanguination
6. Ge.	Cardiac disease	11 weeks	Lap. Trach.	(A) Peritonitis, acute endocarditis
7. Cu.	Cardio-vascular-renal	17 hours	Classic	(A) Cardiac failure, anemia, chronic nephritis
8. Hi.	Placenta previa	16 days	Lap. Trach.	(A) Pulmonary embolism
9. Sz.	Disproportion, diabetes, inertia	10 days	Cesarean-hysterectomy	(A) Peritonitis
10. Le.	Coma, hypertensive encephalopathy	26 hours	Lap. Trach.	Cerebral hemorrhage; eclampsia?
11. Ho.	Pre-eclampsia	29 days	Lap. Trach.	(A) Pulmonary embolism

*A live baby was delivered in each case.
(A) = Autopsy.
"Lap. Trach." = Laparotrachelotomy.
Patients 1 and 2 were delivered by cesarean section only in the interest of the baby.
Patients 3, 4, 5 and 6 died because of lack of experience of the surgeon.
Patient 7 should have had more than one blood transfusion and a longer period of bed rest before delivery.
Patient 8 spotted daily but the obstetrician in charge examined and felt placenta but did nothing for four days. The temperature rose to 39 degrees within twenty-four hours of operation and remained high.
Patient 9 might have lived had a strict peritonitis regime been maintained.
Patient 10 was in deep coma and required no anesthesia for the operation; she was considered moribund.
Patient 11 died of pulmonary embolism and was nonpreventable.

(2.7 per cent); 2. mortality due to operation itself, 185 (4.2 per cent); and 3. mortality due to intercurrent disease, 11 (0.3 per cent). He reported an operative mortality of 5.3 per cent in the University Clinics (total mortality of 8.6 per cent) which is much too high.

Data for individual operators is given in Table IV, and indicates that cesarean section can be performed by specialists with a very low mortality. The figures given for Davis, Hesseltine and myself are for operations either performed by us as surgeon or as first assistant to the resident. We have learned that one must not take chances with the life of a patient. If there are any contraindications to laparotrachelotomy, either cesarean-hysterectomy or vaginal delivery (craniotomy if necessary) is performed.

Data concerning our cesarean deaths, Table V, indicate that poor judgment or lack of skill were responsible for 7 of the 11 deaths.

I have listed in Table VI, the Brooklyn statistics, the maximum mortality rates for various obstetric complications, and the number of

TABLE VI. CESAREAN SECTION MORTALITY FOR VARIOUS COMPLICATIONS

	MORTALITY			
	BROOKLYN, N. Y. 1928		CHICAGO LYING-IN DEATHS	LAPARO-TRACHEL-OTOMY MAXIMUM
	MATERNAL	TOTAL FETAL		
	%	%	NUMBER	%
Obstructing tumors	6.0	4.8	1	1.0
Contracted pelvis, cesarean section	5.8	3.8		0.3
Cesarean section—elective				0.2
Test of labor			1	0.4
Repeat	0.8	7.0	1	0.3
Placenta previa	7.0	19.0	2	2.0
Large fetus and postmaturity	5.4	8.1		0.4
Elderly primipara	15.0			0.4
Eclampsia	27.0	26.0	1	13.0
Nonconvulsive toxemia	7.0	15.0	1	2.0
Abruptio placentae	0.0	63.0	0	5.0
Malposition				0.4
Heart disease	4.8	4.7	2	3.0
Fetal indication				0.2
Previous pelvic operations	4.0	12.0		0.2
Cervical dystocia	4.5	2.0		0.4
Abnormal uterine rings	29.0	29.0		1.0
Total number deaths:	126		9	
Total number operations:	1,759		1,788	

our own deaths. These figures are based on collective studies. One must remember that there is a mortality associated with some of these complications irrespective of the type of delivery. The maximum total mortality rate for cesarean section should be 0.5 to 1.0 per cent, but in the treatment of contracted pelvis, elective cesarean section should have a maximum maternal mortality of 0.2 per cent and after a test of labor, 0.4 per cent.

Indications for Laparotrachelotomy

Elective Indications

1. *Tumors* (uterine or ovarian) blocking the pelvis should have been diagnosed before labor or early in labor.

2. *Contracted Pelvis—Cephalopelvic Disproportion.*—Our practice is to perform an elective cesarean if the true conjugate is less than 8.0 cm., or the transverse diameter of the outlet is less than 7 cm. with the baby estimated to weigh 3,000 grams or more. With the true conjugate greater than 8.0 cm., the patient is given a test of labor. This means that the patient has hard uterine contractions at 3 to 5-minute intervals, lasting at least 35 seconds, for 12 to 18 hours. A maximum of two rectal and two vaginal examinations are made. These patients should have at least one vaginal examination after some hours of labor before they are subjected to the risk of cesarean section. If in this length of time the cervix has not dilated satisfactorily, or the head has not descended to the level of the spines, cesarean section is performed. We do not expect delivery in 24 hours. *Our deadline is 24 hours of ruptured membranes or labor.* In patients who are in labor for a longer period, delivery is effected vaginally, if necessary by craniotomy, or by cesarean-hysterectomy. All statistics show that the bacterial content of the uterus increases progressively after 12 hours of ruptured membranes or of labor, and that if a cesarean section is performed, the morbidity parallels the duration of labor or ruptured membranes. The ideal test

of labor is strong uterine contractions for 1 to 2 hours with complete dilatation of the cervix and ruptured membranes, providing it occurs within the first 24 hours of labor. Unfortunately, many of our patients never reach the second stage even after 36 to 48 hours of labor.

3. *Repeat Cesarean Section.*—Rupture of the uterus has a hospital incidence of 0.05 per cent. Recent reports from maternity hospitals give an average maternal mortality of 40 per cent, range 20 to 80 per cent, and an average fetal mortality of 65 per cent. Various studies of maternal mortality reveal that 6 to 15 per cent of the deaths are due to uterine rupture. Twenty to 100 per cent of the spontaneous ruptures, especially where there was no dystocia, are due to rupture of a uterine scar. Holland reported that after classical cesarean section by experienced obstetricians, the incidence of rupture was 4 per cent, but if labor had commenced the incidence was 19 per cent. The incidence of rupture of the cervical scar is at least 0.3 per cent. These statistics are difficult to obtain. Reports of rupture of the scar rarely give the number of cesarean sections performed, the number who became pregnant again, and, especially those who were delivered vaginally. During the past 13 years, 1,790 cesarean sections were performed by us and only one uterus with a cesarean scar ruptured with escape of the fetus into the abdominal cavity. This patient had been permitted to go into labor and while preparations were being made for operation, the uterus ruptured. In at least six more patients, when the bladder had been separated for a repeat cesarean section, there was found a complete separation of the scar. These patients were not in labor, and there had been no symptoms or signs of the separation, but had labor begun, the fetus would undoubtedly have been extruded into the abdominal cavity. A survey of the literature as well as personal experience indicate that the lower uterine segment scar is less likely to rupture than the classical.

It was thought for many years that uterine incisions heal by regeneration of muscle tissue. Schwarz and his associates have demonstrated both in the experimental animal and in the human that healing takes place by the usual fibrin seal and subsequent proliferation of fibroblasts. There is no way by which the strength of the scar can be detected. Patients have had two vaginal deliveries after cesarean section, and then a uterine rupture with the fourth labor. If the placenta is over the scar, it seems that the incidence of rupture is increased. Therefore, if vaginal delivery is contemplated, an attempt should be made to determine the location of the placenta by x-ray visualization. I can find no evidence that the transverse incision of the lower segment is less likely to rupture. In view of the high maternal and fetal mortality due to uterine rupture and the impossibility of knowing which scars will not rupture, a previous cesarean section in general warrants a repeat operation. It should be performed 7 to 14 days before term. Tubal ligation (hysterectomy in patients past 35) should be advised at the second operation and insisted upon at the third. Catholic patients are best treated by cesarean-hysterectomy after the second or third operation. Physicians have reported six, seven, and even nine cesarean sections on the same patient. In many of these cases the uterus was reported as being adherent to the abdominal wall, which probably accounts for the survival of the patient. Most statistics indicate that the

elective repeat cesarean section has a lower mortality than that of the primary operation. However, cesarean mortality is higher than that after normal vaginal delivery. Therefore, the patient should not be subjected to an unlimited number of cesarean sections.

Some obstetricians do not believe "once a section, always a section," but if they guess wrong, the baby is lost and the mother is subjected to a mortality of 40 per cent, while an elective cesarean section would have subjected her to a mortality of less than 0.5 per cent, and a fetal mortality of less than 2 per cent. We have permitted vaginal delivery only: 1. if the patient entered the hospital in active labor with five or more centimeters' dilatation and no disproportion, 2. if the pregnancy was less than 36 weeks' gestation, or 3. if the baby was dead and then delivery was by craniotomy as soon as there was 8 cm. dilatation.

TABLE VII. PLACENTA PREVIA MORTALITY

HOSPITAL	TOTAL CASES			VAGINAL DELIVERY			CESAREAN SECTION		
		MORT. %			MORT. %			MORT. %	
	NO.	MAT.	FET.	NO.	MAT.	FET.	NO.	MAT.	FET.
Chicago Lying-in	258	0.77	32.0	152	0.00		106	1.88	
Boston Lying-in	548								
Margaret Hague	341	0.58		237	0.88		104	0.00	
Cleveland Maternity	160	0.80	25.0	38	0.00		122	1.65	
Philadelphia Lying-in and Jefferson Maternity	166	6.60			4.90			8.30	
Sloane's and Women's	400	5.30		274	4.70	38.0	126	6.30	11.0
Total:	1,829	2.84		796	2.89		614	2.44	
British-Berkeley	4,580	7.00		818	5.50	68.0	414	4.10	23.4
Collective—Bill				2,117	9.70		262	1.78	
Collective—Mackenzie					8.00	54.0		6.60	17.0
Collective—Kellogg					5.10	63.0		4.00	
Collective—Davis					7.70	57.0		6.50	15.0
Collective—Findley					6.00	57.0		6.00	24.0

4. *Placenta Previa.*—The extensive study by Berkeley of 4,580 cases from leading British maternity hospitals and collective reviews by McKenzie, Findley, Davis, Irving and Bill, as well as the results from several American maternities are given in Table VII. These data show that vaginal delivery is accompanied by a maternal mortality ranging from 0 to 11 per cent with an average of 6 for all hospitals and 3 per cent for maternity hospitals. Delivery by cesarean section has a range of 0 to 11 per cent with an average of 4 per cent for all hospitals and 2.4 per cent for maternity hospitals. The cause of death in placenta previa is either from hemorrhage or from infection. If vaginal delivery is carried out, only the most expert care will prevent tears in the fragile lower uterine segment. Kellogg and Irving state that the inexperienced physicians have a lower maternal mortality with cesarean section than with vaginal delivery. I qualify this by adding if rupture of the membranes does not control the bleeding. If the insertion of a bag or Braxton Hicks version are required to control the hemorrhage, Watson's studies showed that 69 per cent of the cases required a serious operative delivery. It is disappointing to note that only 5 to 20 per cent of the patients received blood transfusions, and many authors and reviewers commented that the patients were not given enough blood, especially after delivery. Death from hemorrhage is again the old story of too

little and too late. Our practice is to classify the case as a *complete* placenta previa if the internal os at the time of the examination, irrespective of the amount of dilatation, is completely covered with placental tissue, and *incomplete* if the os is only partially covered. Any patient who is 30 weeks or more pregnant with complete placenta previa is best treated by cesarean section. Approximately 25 per cent of the patients fall in this class. It is difficult to lay down any hard and fast rules, but in general, cesarean section is the operation of choice in the treatment of placenta previa. Where the placenta is palpated one or more centimeters from the os, or where it cannot be palpated but is said to be low lying, vaginal delivery can usually be safely carried out. Early and repeated transfusions will aid in decreasing maternal mortality.

Diagnosis of Placenta Previa Is by Vaginal Examination.—Visualization of the placenta by x-ray is not perfect or always feasible, nor does it give information as to the degree of previa.

Irving, Greenhill and Davis believe that the incidence of fetal monstrosities is increased in patients with placenta previa. Murphy could find no significant increase. This possibility should not deter one from performing cesarean section. The mother's life is of paramount importance.

DeLee repeatedly stated that the lower segment operation was especially indicated in cases of placenta previa because one could suture bleeding maternal sinuses. If the placenta is on the anterior wall, bleeding from the low cervical incision is controlled only with great difficulty. Therefore, many obstetricians perform the low classic incision because there is less operative hemorrhage.

The gynecologist has known for many years that the incidence of peritonitis after myomectomy if the uterine cavity is opened is markedly increased in those patients who have had persistent uterine bleeding for days. This increased susceptibility to infection is due chiefly to the increased bacterial count (possibly increased virulency) caused by the constant presence of blood in the vagina. Thus, the patient who has been bleeding from placenta previa for days is quite likely to develop a puerperal infection after cesarean section even if no examinations are made. Vaginal instillations should be used. Hysterectomy may be necessary.

5. *Breech presentations* in patients with contracted pelvis or in elderly primipara with large babies warrant elective cesarean section.

6. *Transverse presentations* in primipara and recurrent transverse presentations in multipara are frequently best treated by elective laparotrachelotomy.

7. *Heart Disease.*—Patients who have fully recovered from cardiac decompensation during pregnancy are occasionally delivered by cesarean section at a time thought most opportune.

8. *Previous Operations.*—Extensive vaginal or cervical plastic operations and previous radium application to the cervix frequently necessitate laparotrachelotomy.

9. *Fetal.*—Elective cesarean section is justified in the interest of the baby in some patients, although it increases the risk for the mother

(elderly primipara, previous sterility, low fertility, previous repeated stillbirths, fetal asphyxia in early labor). This is especially true if there are several major complications present.

Relative Indications

1. *Large Fetus—Postmaturity.*—The incidence of postmaturity is approximately 7 per cent and of fetuses weighing over 4,500 grams is 1 per cent. There is a definite correlation between postmaturity (294+ days) and fetuses weighing over 4,000 grams. The length of labor, incidence of cesarean section and fetal and maternal mortality are definitely increased. Postmaturity, if the menstrual history is correct, should cause no concern, providing there is no disproportion or other complications. A large fetus, as determined by abdominal palpation or measurement (McDonald or Ahlfeld method), is always of concern. No attempts at inducing labor should be instituted. When spontaneous labor begins, it must be conducted as a "test of labor." Stereoscopic anteroposterior and lateral x-ray films during labor may be of diagnostic value.

2. *Elderly Primipara.*—Consensus of opinion defines elderly primipara as patients who have their first child when they are 35 years of age or over. Kuder and Johnson report an incidence at the New York Hospital of 2.7 per cent. They noted an increase incidence of toxemia, contracted pelvis (especially funnel), prolonged labor, myoma and an increased maternal and fetal mortality. Our practice in these patients near term is, if possible, to permit our usual test of labor. If the membranes rupture prematurely, and if labor cannot be started with fractional doses of pituitrin, and if the pelvis is empty, we will perform a cesarean section within 24 hours.

3. *Toxemia of Pregnancy.*—The mortality from cesarean section in the treatment of eclampsia ranges from 2 to 88 per cent. This is readily understandable when one realizes that the mortality in the United States for cesarean section is approximately 5 per cent, and for eclampsia is 13 per cent. It is obvious that the expert obstetrician will have a very low mortality from cesarean section, even when the patient has eclampsia, if the latter has first been treated medically. The indiscriminate use of cesarean section in the treatment of eclampsia or operations by inexperienced surgeons results in mortality rates that are appalling. Cesarean section is indicated in toxemic patients if there is cephalopelvic disproportion. In pre-eclampsia where the blood pressure, proteinuria and edema are increasing despite treatment, or where symptoms develop and the cervix is not effaced, an elective cesarean section is indicated. Only the patient with the *severe type of eclampsia and an uneffaced cervix should after 8 to 12 hours of proper medical treatment be delivered by cesarean section.* The patient is certainly a better risk for operation at this time, than if one waits until she is moribund and then attempts to save her by cesarean section. Patients with mild eclampsia are treated medically for days until the cervix is effaced. Approximately 40 per cent of the patients have antepartum eclampsia, but only one-fourth of the cases is severe. During the past thirteen years, we have treated 86 patients with eclampsia and cesarean section has been performed in only 12 (14 per cent). In some of these, the operation was performed on account of disproportion, or the convulsions occurred after the delivery.

Approximately 11 per cent of our patients with pre-eclampsia and 21 per cent with vascular-renal diseases are delivered by cesarean section. It is the method of choice in patients with severe vascular or renal disease if the pregnancy has to be terminated between 32 and 38 weeks in the interest especially of the fetus. Tubal ligation (sterilization) per se is not an indication for cesarean section.

In the period under report, there were 241 (7.0 per cent) cesarean sections in 3,102 patients with nonconvulsive toxemia. In many of these patients, there have been several indications for cesarean section, none alone being sufficient, but the combined indications warranted the operation.

TABLE VIII. ABRUPTIO PLACENTAE MORTALITY

HOSPITAL	TOTAL CASES			VAGINAL DELIVERY			CESAREAN SECTION		
		MORT. %			MORT. %			MORT. %	
	NO.	MAT.	FET.	NO.	MAT.	FET.	NO.	MAT.	FET.
Chicago Lying-in	225	1.33		156	1.92		69	0.0	
Margaret Hague	414	0.48		342	0.58		72	0.0	
Boston Lying-in	353	11.30		252	11.50		99	11.0	
New York Lying-in	93	3.20							
Total:	1,085	4.40		750	4.50		240	4.6	
Collective—Bland	2,319	6.30	66.0	414	4.10	61.0	107	11.2	74.0
Collective—Irving		5 to 10	60 to 90						
Collective—Weymeersch			63.0		6.60	61.0		21.0	70.0

4. *Abruptio Placentae.*—Collective reviews by Bland and Rakoff, and Irving reveal that the maternal mortality ranges from 0 to 18 per cent with an average of 6.3, and the fetal mortality ranges from 55 to 100 per cent with an average of 66 per cent. The average maternal mortality for vaginal delivery was 4.1 per cent and for cesarean section was 11.2 per cent. The data in Table VIII, from four maternity hospitals gives an average maternal mortality of 4.4 per cent. The maternal mortality for patients treated by cesarean section was 4.6 per cent and by vaginal delivery 4.5 per cent. The consensus of opinion, with the exception of Irving, is that patients presenting evidence of deep shock, low hemoglobin, rapid pulse, a uterus larger than the period of gestation; and one in which dilatation of the cervix does not occur after the membranes have been ruptured for 6 to 12 hours, are best treated by cesarean section. During the period of observation large amounts of blood, as well as 2,000 to 4,000 c.c. of parenteral glucose and saline solutions must be given. Irving states that he has seen no postpartum hemorrhage from the so-called Couvelaire uterus. Various authors have reported on the continued bleeding from the uterus after delivery; and DeLee, in 1901, made note of the hemophiliac-like nature of some of these cases and stated that the blood failed to clot in two. Davis and McGee reported that in 10 of the 12 fatalities in their series, death was due to continued bleeding from the uterus, which could not be controlled by an intrauterine pack or by clamping the uterine arteries in two cases. We have had to remove two uteri, 2 and 6 hours, respectively, after delivery because of persistent hemorrhage. We have shown that the blood fibrin may be absent or may be reduced to such a low concentration that proper coagulation cannot occur. If the obstetrician is in doubt about possible postpartum hemorrhage, hysterectomy is advised.

Borderline Indications

1. *Breech Presentations.*—Borderline pelvis, large babies and/or faulty labor may require laparotrachelotomy after a test of labor.

2. *Malposition.*—Face and brow presentations in which dilatation is slow or fails to occur, or the head fails to engage, should be treated as cases for tests of labor and delivery if necessary effected by cesarean section.

Cesarean section followed by oophorectomy, hysterectomy or tubal ligation is a proper procedure. Myomectomy, if the tumors are in the line of incision, is indicated. Other myomas should be left alone until after the patient has her family. Hysterectomy is indicated if the tumors are numerous, or if any are 10 cm. or more in diameter. Cesarean section followed by appendectomy, cholecystectomy, etc., is indefensible and will result in increased maternal mortality.

Fetal Mortality.—The purpose of obstetrics is to ensure a live undamaged mother and baby. Cesarean section does not always accomplish this. The stillbirth and neonatal mortality are definitely increased after 24 hours of labor or ruptured membranes. Many babies survive after prolonged labor, but the incidence of brain injury is increased as a result of intracranial hemorrhage or intrauterine asphyxia. A normal fetal heart rate after prolonged labor will not always ensure a living, undamaged baby. Craniotomy, even on the living but potentially damaged fetus, is a better procedure than cesarean section after prolonged labor which not infrequently terminates in both maternal and fetal death.

Types of Cesarean Section

The increased possibility of puerperal infection after cesarean section as compared with vaginal delivery has been known for decades. I have listed in Table IX, the various types of cesarean section together with some recent mortality figures for each type of operation. Each modification has been designed to lower the maternal mortality.

TABLE IX. MORTALITY FOR VARIOUS TYPES OF CESAREAN SECTION

HOSPITAL	CLASSICAL		LOW CERVICAL		EXTRAPERITONEAL		CESAREAN-HYSTERECTOMY	
	NO.	M.M. %	NO.	M.M. %	NO.	M.M. %	NO.	M.M. %
					250 Waters	0.80		
Margaret Hague	117	6.8	1,261	1.03	181 Latzko	1.65	27	7.40
Boston Lying-in	372	2.1	168	4.20	23	0.00	21	14.30
Women's, N. Y.	235	4.3	620	2.10	34	2.94	17	5.90
Chicago Lying-in	22	18.1	1,618	0.38	1	0.00	96	1.04
Total:	746	4.0	3,667	1.07	489	1.23	161	4.30
Collective, Irving	3,334	6.7	2,006	1.85	391	4.00	212	10.40

Bacteria from the vagina gain access to the uterus during prolonged labor and during the postpartum period. Certainly by the end of the second postpartum day, all uteri contain bacteria which have usually come from the vagina. The natural resistance of the woman is her only protection against these bacteria; and she is especially resistant against those from her own vagina unless these bacteria are given special opportunities to invade, such as would occur in prolonged

labor, excessive manipulation, excessive blood loss or the retention of a piece of placenta. The postpartum uterus containing a large wound (placental site) blood clot, bacteria, and having a poor blood supply is an excellent culture tube. The experience has been that patients dying from infection after classical cesarean section usually have some separation of the uterine incision with drainage of the lochia into the abdominal cavity. Quite obviously, cesarean-hysterectomy in potentially or actually infected patients offers the best chance for their recovery. As seen from the table, the maternal mortality after cesarean-hysterectomy ranges from 1 to 14 per cent with an average of 4.3 per cent. There is no question but what the mortality would have been much higher had these uteri not been removed. The institution of a "peritonitis routine" immediately after operation and its maintenance for two or more days, or its institution as soon as the patient shows fever, tachycardia, vomiting or distention, would have undoubtedly reduced the mortality in some of the cesarean-hysterectomies.

Careful details as to vaginal preparation and the prevention of spill (in other words, much the same management that one would use in a total hysterectomy for carcinoma of the corpus) will lessen the likelihood of serious postoperative infection. One hesitates to perform cesarean-hysterectomy with the first baby. Here, the operation of choice might be craniotomy. However, a live patient without a uterus is a better result than a dead patient with a uterus.

The extraperitoneal, low cervical cesarean and other modifications have been designed to prevent the possible drainage of uterine contents into the abdominal cavity. The extraperitoneal was the first modification suggested and is theoretically ideal. Baldwin's results in the treatment of puerperal infection by hysterectomy prove conclusively that extraperitoneal section is not as safe as cesarean-hysterectomy. The data in the table indicate that the average maternal mortality for extraperitoneal section is 2.5 per cent, ranging from 0.8 to 4 per cent. Unfortunately, the majority of these patients were not infected or even potentially infected. For example, Waters states that most of their extraperitoneal sections are done for teaching purposes. This operation is dependent for its safety upon an uninjured parietal peritoneum. Any perforation, even if ligated, destroys the safety of the operation. I believe a careful study by any one of the published statistics, Table IX, as well as discussions with some of the advocates, will clearly show that this operation is not the proper treatment for the infected case.

The low cervical incision was developed to increase the safety of cesarean section by placing the uterine incision beneath the bladder peritoneum. Statements were made that since the incision was in the quiescent portion of the uterus, better healing would result. The incision can be sutured more easily than the classical incision. The safety of the operation, however, depends upon the fact that the incision is covered with a peritoneal flap which, if it has been properly sutured, will become adherent within hours and thus prevent leakage of lochia into the abdominal cavity should it occur through the uterine incision.

Marsupialization of the uterus and exteriorization of the uterus have no place in modern obstetrics.

The low cervical incision as a routine type for cesarean section results in less morbidity and less mortality than any other type of cesarean section and should be practiced by anyone performing abdominal delivery after the thirty-fourth week of pregnancy with the possible exception of cases of placenta previa or where time is a factor. In these two latter conditions, if the case is not potentially infected, classical cesarean section with proper peritonization of the uterine incision (Schumann's modification) offers the best results.

Morbidity and Puerperal Infection

The usually accepted standard of morbidity is temperature elevation. Unfortunately, other complications such as tachycardia, shock, hemorrhage, early death (before fever can develop), ileus, anemia, vomiting, etc., are not included. Many institutions take the temperature only twice daily. Their morbidity will be less than where the temperature is taken more frequently. The morbidity after cesarean section ranges from 20 to 60 per cent. The total obstetric morbidity for three maternity hospitals has been approximately 10 per cent. The incidence at our hospital for one year, of temperature elevations up to 38.9 degrees, was 5.5, and over 39 degrees, was 3.4 per cent; a total morbidity of 8.9 per cent. The incidence of serious puerperal infection was 0.4 per cent. The morbidity in the first 500 cesarean sections at our hospital was 47 per cent, in the second 500 it was 41 per cent, and in the third 500 it was 31 per cent, an average of 40 per cent for the whole group. This morbidity after laparotrachelotomy is rarely associated with sick patients such as were encountered after classical section. Vomiting and distention occurred in less than 5 per cent of our cesarean patients. We attribute this to: A. the prevention of spill (meconium, blood and amniotic fluid) into the abdominal cavity, B. limited vaginal (2) or rectal (2) examinations in patients who may be subjected to operation, and C. the use of local anesthesia.

Vaginal instillations of a 2 per cent aqueous solution of mercurochrome were started by Mayes in 1924. He reports that in the Methodist Hospital in Brooklyn with instillations they had only two deaths from puerperal infection during the delivery of 24,392 patients as compared with 25 deaths from infection during 10,368 deliveries without instillations. I instituted vaginal instillation of mercurochrome in glycerin on the Washington University obstetric service in 1926. In 1931, a change was made to 1 per cent acriflavine in glycerin. T. K. Brown reports that on this service 8 c.c. of the solution are instilled with an asepto syringe every four hours during labor and before each rectal or vaginal examination. Patients who may be delivered by cesarean section are instilled once daily. Patients with ruptured membranes but not in labor are instilled twice daily. He states that there were 13 maternal deaths from sepsis between 1924 to 1932 (9,539 deliveries) and no deaths from infection without the use of chemotherapy from 1932 to 1941 (14,789 deliveries).

Harris and Brown obtained uterine cultures from 50 patients at section. Anaerobic growth was obtained in 45 per cent of the positive

cultures. "No sterile cultures were obtained from patients in whom active labor had lasted for six hours or more."

T. K. Brown reported that in a series of 144 cesarean sections studied at the St. Louis Maternity Hospital, the incidence of positive uterine culture was only 4.1 per cent when vaginal instillations of acriflavine were employed; and that since 1931, puerperal infection as the cause of mortality associated with cesarean section has been eliminated, apparently due to the use of antiseptic vaginal instillations.

Various investigators have confirmed the report first published by Schottmüller in 1910, and reiterated by Schwarz and Dieckmann in 1926, that over two-thirds of the cases of puerperal infection on clean obstetric services are due to anaerobic streptococci. These infections are autogenous, resulting from prolonged labor, prolonged rupture of membranes, excessive trauma at delivery, retention of a piece of placenta, lack of uterine tone. No drug to date has been found to be effective in the cure of anaerobic streptococcal infection. *Prevention is easier than cure.*

Since 1931, at the Chicago Lying-in Hospital, we have been using one per cent acriflavine in glycerin with each vaginal examination. On April 1, 1943, we substituted 1 to 1,000 merthiolate in glycerin and in addition, began making vaginal instillations of 8 c.c. every 8 hours after 12 hours of labor or ruptured membranes. Elective cesarean sections are instilled the night before, morning of operation and when the uterine packing is removed.

Vaginal instillations of an antiseptic solution are not comparable to the douches, etc., used 40 years ago. The studies to date demonstrate the value of these treatments. Until someone has shown conclusively that vaginal instillations are of no value, they should be used in patients who may be delivered by cesarean section (trial labor), in cases of prolonged labor, and in patients with premature rupture of membranes.

Reproductive History After Cesarean Section

Bride, in 1921, followed-up 190 patients who had had a cesarean section; 94 had 106 pregnancies (17 of which aborted); 66 used no contraceptives, and he concluded that there was a relative sterility of 41 per cent.

Schmelzer, in 1940, studied the fertility in 90 patients who had had a cesarean section; 83 patients had 158 pregnancies, 26 terminated by abortion, 45 by repeat section, and 87 by vaginal delivery. He concluded that cesarean section did lower the fertility slightly, especially if the first pregnancy was terminated by section.

We have not made a statistical study of subsequent pregnancies, but doubt if a relative sterility does result from cesarean section. Almost one-third of our cesarean sections was performed because of previous cesarean section. If there has been no serious endometritis, subsequent fertility is normal.

Anesthesia

Some type of anesthesia is necessary for cesarean section even though it adds to the risk. However, the obstetrician should limit himself to the use of one or two anesthetics and leave experimentation with new

anesthetics to the large clinics. Eleven, 4 per cent, of the cesarean deaths in Massachusetts over a five-year period were due to anesthesia.

Local anesthesia using one-half per cent novocain is the safest anesthetic. Sixty per cent of our operations are performed with it, and an additional 15 per cent are combined local anesthesia and inhalation. To date, we have had no maternal or fetal deaths, or complications which could be attributed to the local anesthesia. Even if a general anesthetic is to be used our chief anesthetist, Dr. P. Ouda, has demonstrated that the duration and depth of the anesthesia can be decreased if local infiltration is carried out prior to the general anesthetic. Many obstetricians use local anesthesia supplementing with gas anesthesia during the delivery of the fetus. Morphine 0.01 to 0.016 Gm. will have an immediate effect, if given intravenously as the baby is delivered.

Synephias in 1939, commented on anesthetics for cesarean section as follows: 42 deaths and 6 serious accidents occurred with evipal; there were no deaths in over 4,000,000 anesthetics for delivery using nitrous oxide, ethylene or cyclopropane; spinal anesthesia is excellent except the dangers increase as term is approached; local anesthesia is innocuous and excellent, but it may not suffice if the patient is in active labor.

Inhalation.—Since 1931, there have been over 46,000 obstetric anesthetics given at our hospital by trained physicians with some 45 aspirations during anesthesia with ethylene or cyclopropane and ether with two maternal deaths, both patients dying within 24 hours. Eight more patients were seriously ill but recovered. There have been no cesarean deaths from anesthesia, but there have been some serious cases of bronchopneumonia. Drop ether is the safest of the inhalation anesthetics. Chloroform is used by very few obstetricians, but if properly given is ideal for the delivery. It should not be used for repairs or for prolonged operative deliveries. Ethylene or nitrous oxide and ether are next in safety. There is some evidence indicating that cyclopropane is more hazardous for baby and mother, in the latter predisposing to shock, and in the former to anoxemia.

Only a liquid diet is permitted during labor and nothing is given by mouth within 6 hours of a general anesthetic. If patients have recently eaten, the stomach contents are aspirated by tube.

Intravenous.—Evipal and other intravenous anesthetics entail a definite risk because of the pregnancy (labile blood pressure, marked and sudden changes in intra-abdominal and intrapulmonary pressures).

Rectal.—Avertin as a preliminary anesthetic has an increased hazard in pregnancy as mentioned in the preceding paragraph. Ether in oil is a safe supplemental anesthetic, if there is no one capable of administering an inhalation anesthetic.

Spinal.—A number of obstetricians advocate spinal anesthesia for cesarean section. At the Margaret Hague Maternity the only contraindication is arteriosclerosis. Cosgrove and Waters use it for patients in shock. Watter also advocates spinal anesthesia in patients who are in shock. However, most anesthetists who use spinal anesthesia warn of its dangers in patients with abnormally low or high blood pressure, or seriously sick patients. In these, they advise the use of local anesthesia.

The fatalities from spinal anesthesia in pregnancy are due to the lability of the blood pressure which reaches a maximum at term. One can collect several thousand cesarean sections performed under spinal anesthesia without any maternal mortality. However, Franken has collected 2,000 cesarean sections under spinal anesthesia with 14 deaths. If the blood pressure decreases to the shock level and persists for five minutes or longer, it may cause cerebral injury in the fetus as a result of the anoxemia. We have had one baby with cerebral injury due to prolonged shock (the mother had received no anesthesia), and one similar case has been reported after continuous caudal anesthesia, as well as one fetal death.

Marshall, Ginglinger, Brindeau, Synephias and numerous other obstetricians, although using spinal anesthesia themselves, warn of the increased risk, especially during pregnancy.

Caudal anesthesia by either a single or continuous injection entails the same dangers for mother and fetus as does spinal. Hingson has recently reiterated the dangers and contraindications for caudal anesthesia.

Our belief is that if the obstetrician has no one capable of administering an inhalation anesthetic and he is not able to perform the operation under local anesthesia, spinal anesthesia, using 80 to 100 mg. of novocain and preceded by one injection of 0.048 Gm. ephedrine, should be used. Oxygen administration may be necessary for both spinal and caudal anesthesia until the fetus is delivered.

Special Points in Technique

Spill of amniotic fluid, blood and especially meconium should be prevented by use of suction and packs. The latter cannot be properly used with local anesthesia. Spill into the abdomen is retarded by the first assistant maintaining constant tension on the traction suture, placed at the upper end of the uterine incision, or the uterus may be sutured to the abdominal wall. In patients who are not in labor, the uterine incision must be extended in most instances into the contractile portion of the uterus for 2 to 4 centimeters. If the visceral peritoneum is reflected by an elliptical incision (as used for advancement of the bladder) in place of a transverse incision, and only one flap is raised, beginning as high on the uterus as feasible, the uterine incision can be covered by this peritoneum using a tight running suture of zero chromic catgut. Additional safety is assured by a second suture line (Lembert). Thus, within 24 hours the uterine incision is sealed off from the abdominal cavity. Patients who have fever, distention, tachycardia, vomiting or excessive spill should be placed on a "peritonitis routine" (nothing by mouth, and at least 1,000 c.c. saline and 2,000 c.c. of 5 or 10 per cent glucose solution parenterally every 24 hours) for 48 hours or longer depending on the postoperative course.

The uterine incision is closed in two layers, using interrupted sutures of zero chromic for the first layer and continuous for the second. The sutures should be 1 cm. apart and not tied too tightly. The fundus of the uterus is *always* firmly packed with gauze, with only a strip of the gauze in the lower segment and vagina. This pack is inserted not to prevent hemorrhage, but to ensure a maintenance of uterine tone which

will favor the formation of the fibrin seal in the incision and promote the drainage of the lochia. The gauze is removed in 8 hours.

Daily and Dieckmann reported that the average blood loss at cesarean section by competent surgeons is 539 c.c. (range 100 to 1,410). This amount of blood with vaginal delivery is usually regarded as a postpartum hemorrhage. It was less if patients were in labor, or if 0.5 c.c. of solution of posterior pituitary was injected into the uterus after delivery of the head and after 30 seconds the fetus extracted very slowly.

Five cesarean deaths in Massachusetts in 1941, were due to transfusion accidents. These are preventable deaths. During the past year, two of our patients received incompatible blood but did not die. The fault was the lack of experience by our residents, and while we have instituted all precautions possible, we are also giving one-third less blood transfusions than we did two years ago. Naturally, if there has been extensive hemorrhage, enough blood is given in as short a period as possible to maintain a hemoglobin concentration of at least 10 grams. If time is available 4.0 Gm. $NaHCO_3$ are given every two hours, for 8 doses, beginning at least 12 hours before the transfusion. If there is any suspicion of an incompatible blood, 300 c.c. of molar sodium lactate are mixed with 2,700 c.c. 5 per cent glucose; 1,500 c.c. are given intravenously and the remainder by clysis.

Summary

Laparotrachelotomy in patients with cephalopelvic disproportion can be performed with a maximum maternal mortality of 0.2 per cent as an elective operation and 0.4 per cent after a test of labor (with our criteria). Other indications are usually accompanied by an increased maternal mortality, but the increase should be due to the complication and not to the operation.

Total cesarean section mortality can be kept below 1 per cent by the following evaluation of the case:

1. Is there a proper indication—elective, relative, or borderline?

2. Are there any of the following contraindications present? (a) Ruptured membranes over twenty-four hours. (b) Labor over twenty-four hours. (c) Repeated rectal or vaginal examinations. (d) Operative manipulation either for induction of labor or for delivery. (e) Uterine infection. (f) A dead or damaged fetus.

3. Will another procedure, usually a craniotomy, assure a lower maternal mortality?

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Discussion

DR. ROLAND S. CRON, MILWAUKEE, WISCONSIN.—This is a very masterful presentation of the cesarean section problem. It is most complete and we subscribe to its principles almost without exception.

In the matter of vaginal and rectal examination, we differ with him. We prefer to have the patient experience five or six rectal rather than one or two vaginal examinations. We do not routinely pack the uterus after cesarean section as Dr. Dieckmann advocates. The vast majority of cesarean sections in Milwaukee are done under general anesthesia. In Milwaukee only 25 per cent of all the deliveries in the State occur, while 50 per cent of all cesareans are done there.

A study of the cesarean statistics from the Milwaukee County Health Department and five large hospitals with maternity departments, during the years 1939 to 1943, inclusive, shows a marked increase in hospital deliveries so that, in 1943, 10,316 of the 11,556 deliveries were cared for in hospitals. Maternal mortality, however, in 1943, jumped to 3.3 from a previous 1.4 per 1,000 deliveries. Does this mean less satisfactory maternal care since the Armed Services have deprived us of so many obstetricians? It is also interesting to note that one-third of all maternal deaths were complicated by cesarean section. For example, during 1940 the incidence of section in Milwaukee County had reached 6.4 per cent with the very high rate of 9.4 per cent for all hospital deliveries. Realizing that too many women were being sectioned needlessly, a group of obstetricians decided to correct this situation. Accordingly, consultation by a member of the staff of each institution was demanded before operation. The results were most astounding. Without exception, the incidence in the three institutions where such a rule was adopted was immediately reduced by 50 per cent so that, during the past two years, the rate had been reduced to a low of 2.2 per cent in the County, and 9.6 per cent in a private hospital with an acceptable average of about 4.8 for the controlled group of institutions. Even with this remarkable reduction there has been no increase in fetal mortality. The maternal mortality for cesareans during the years 1940 to 1943, after consultation service had been established, showed 2 deaths in 853 cesarean sections, an incidence of 0.23 per cent. When one realizes that 40 per cent of these cesareans were done by general surgeons or practitioners, and a very high percentage done under general anesthesia, it appears that the contraindications had been observed and that the higher the incidence of sections the lower will be the mortality rate.

SERUM PROTEIN IN NORMAL AND TOXEMIC PREGNANCY*

ROBERT E. RINEHART, M.D.,† ROCHESTER, MINN.

(From the Department of Biochemistry, University of Oregon Medical School, Portland)

A LOWERED concentration of total plasma or serum protein during pregnancy has been reported by numerous investigators.[1-22] The study by Plass and Matthew[14] is the most complete in the literature on this subject. They found that during normal pregnancy the concentration of plasma protein begins to fall during the third lunar month, or occasionally even before that time, and decreases gradually to a minimum at the ninth month. Thereafter, there is a slight rise, with values at the tenth month still somewhat below normal. A further sharp increase occurs at the time of labor but in the next forty-eight hours the concentration of protein suffers an abrupt decrease, followed by a gradual rise to normal about one week after labor. Fewer studies

*Originally submitted to the Department of Biochemistry and The Graduate Division of the University of Oregon Medical School in partial fulfillment of the requirements for the degree of Master of Science.

†Now a Fellow in Medicine of the Mayo Foundation, Rochester, Minnesota.

of protein fractions during pregnancy have been made.[3-6, 8, 9, 13-20] Most investigators have reported that the concentration of serum albumin closely parallels that of the total serum protein and is responsible for the changes noted.

This study was undertaken because of the possible relationship between the concentration of serum protein and the mild, so-called physiologic, edema of normal pregnancy and the severe edema and albuminuria of pre-eclampsia. Strauss[16-20] has discussed this problem at length and presented a great deal of evidence indicating that many of the symptoms of eclamptogenic toxemia are initiated by a lowered concentration of serum protein.

Methods and Material

The concentration of total serum protein was determined by the colorimetric biuret method of Robinson and Hogden.[23] The albumin was separated by Kingsley's[24] procedure and its concentration determined in the same manner. A Klett-Summerson photoelectric colorimeter was used throughout the study. The determinations were frequently checked by Kjeldahl analysis of aliquot portions and the results were always within the limits of experimental error. Blood was drawn without stasis, allowed to coagulate, and the serum analyzed within twenty-four hours.

The average and extreme values for thirty-one healthy nonpregnant student nurses, which are considered to cover the "normal" range, were as follows: Total serum protein, average value 6.94 Gm. and extreme values 6.6 and 7.3 Gm. per 100 c.c. respectively. Albumin, average value 4.96 Gm. and extreme values 4.7 and 5.2 Gm. Globulin, average value 1.99 Gm. and extreme values 1.5 and 2.4 Gm.

The average and extreme values for thirty healthy male medical students were similar but somewhat higher. The average value for total serum protein was 7.55 Gm. and the extreme values were 6.9 and 8.6 Gm. The average value for serum albumin was 5.01 Gm. and the extreme values were 4.0 and 5.8 Gm. The average value for serum globulin was 2.47 Gm. and the extreme values were 1.6 and 3.8 Gm. The spread of the extreme values here probably represents variations in environmental factors, not encountered so often in the group of nursing students. It is quite clear, however, that the average and extreme values for men tend to be significantly higher than those for women.

Subjects were selected from the patients attending the prenatal clinic. All patients who had systemic disease accompanying pregnancy were excluded from the series. Patients included in the toxemic group were selected according to the criteria of Strauss,[20] which were stated as follows: "The clinical picture manifested by these women is characterized, first, by the absence of apparent abnormalities before gestation and after the puerperium, and second, by a fairly typical course. In the last trimester of pregnancy a rapid gain in weight, generally but not always manifest as edema, is followed by a rising blood pressure, albuminuria, gastric pain, convulsions, and coma."

All dates were calculated from the actual date of delivery when this could be ascertained; in a few cases the date of expectancy was used.

For convenience the data have been classified on the basis of parity, season, and degree of toxemia. They further are subdivided under total protein, albumin, and globulin. The value for fibrinogen was not determined.

Normal Pregnancy

A total of 251 determinations of the concentration of total serum protein was made on seventy-nine normal pregnant women. Table I

TABLE I. SERUM PROTEIN VARIATIONS DURING NORMAL PREGNANCY

PERIOD	DETERMINATIONS	TOTAL SERUM PROTEIN, GM. PER 100 C.C.		SERUM ALBUMIN, GM. PER 100 C.C.		SERUM GLOBULIN, GM. PER 100 C.C.	
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Postpartum, days	23	5.7 to 7.5	6.8	3.7 to 5.3	4.4	1.7 to 3.2	2.4
Delivery to 20*	48	5.9 to 7.5	6.6	3.5 to 4.7	4.0	1.6 to 3.4	2.5
21 to 40	34	6.0 to 7.7	6.5	3.7 to 5.3	4.2	1.4 to 3.0	2.2
41 to 60	31	5.9 to 7.2	6.5	3.7 to 4.6	4.0	2.1 to 3.1	2.4
61 to 80	25	6.0 to 7.5	6.6	3.6 to 4.6	4.2	1.9 to 3.5	2.5
81 to 100	18	5.8 to 7.7	6.5	3.6 to 4.7	4.3	1.0 to 3.1	2.4
101 to 120	10	5.9 to 7.4	6.7	3.4 to 4.8	4.3	1.8 to 3.1	2.4
121 to 140	11	6.2 to 7.3	6.6	3.8 to 5.3	4.4	1.5 to 2.7	2.2
141 to 160	10	5.9 to 7.5	6.6	4.1 to 5.2	4.4	1.7 to 2.5	2.2
161 to 180	10	6.1 to 7.3	6.6	4.0 to 4.7	4.4	1.2 to 2.9	2.2
181 to 200	10	6.1 to 7.7	6.7	4.2 to 5.3	4.6	1.8 to 2.5	2.2
201 to 220	14	6.1 to 7.4	6.7	3.8 to 5.8	4.7	1 6 to 2.6	2.2
221 to 250	8	6.5 to 7.3	7.0	4.5 to 5.0	4.7	2.0 to 2.8	2.3
	Total 251	Average	6.7	Average	4.4	Average	2.3

*Days prepartum.

TABLE II. SEASONAL VARIATIONS IN CONCENTRATION OF SERUM PROTEIN DURING NORMAL PREGNANCY

PERIOD	DETERMINATIONS	TOTAL SERUM PROTEINS, GM. PER 100 C.C.		SERUM ALBUMIN, GM. PER 100 C.C.		SERUM GLOBULIN, GM. PER 100 C.C.	
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Dec.-Jan.-Feb.	12	6.7 to 7.8	7.3	4.6 to 5.7	5.0	1.0 to 3.1	2.3
Mar.-Apr.-May	114	6.0 to 7.5	6.6	3.5 to 5.1	4.2	1.7 to 3.4	2.4
June-July-Aug.	109	5.5 to 7.5	6.6	3.4 to 5.8	4.3	1.3 to 3.5	2.3
Sept.-Oct.-Nov.	43	6.0 to 7.5	6.8	3.6 to 5.0	4.3	1.7 to 3.4	2.5
	Total 278						

shows the variations observed in this group. It will be noted that the average value for globulin remained almost constant throughout. At all times it was slightly higher than that for normal nonpregnant women. The concentration of total serum protein tended to fall to a minimum during the eighth and ninth months but rose rapidly toward normal after delivery. The values ranged between 5.7 and 7.7 Gm. per 100 c.c.; the average value was 6.7 Gm. The lowest average value represented a decrease of 7.1 per cent from the average for nonpregnant women, compared with a 9.3 per cent decrease noted by Plass and Matthew.[14] The most marked changes were found in the albumin fraction. The concentration of albumin fell from an average of 4.7 Gm. per 100 c.c. of serum at the beginning of the study (average normal value for nonpregnant women 4.9 Gm.) to 4.0 during the eighth and ninth months, a decrease of 18 per cent from the average normal value for nonpregnant women. Plass and his associates[13, 14] found a decrease of 13.5 per cent in this fraction. In the thirty-one nonpregnant women studied, the albumin constituted 72 per cent of the total protein, whereas at its lowest point in the pregnant series it constituted 62 per cent, a decrease of 14 per cent.

Since it seemed that the concentration of serum protein might be

related to the parity of the subjects, the values obtained for the primiparas in the series were plotted separately. The curves obtained coincided almost exactly with those plotted for the entire group. The concentration of serum protein, expressed in grams per 100 c.c., were as follows: total protein, average 6.7, range 5.8 to 7.7; albumin, average 4.4, range 3.6 to 5.9; globulin, average 2.3, range 1.0 to 3.1.

Since it has been shown by Dodd and Minot[25] that the concentration of serum protein of persons in a given geographical region tends to vary with the season, the values were replotted according to the month in which the specimens were taken, without regard for the duration of the pregnancy. These are shown in Table II. It is obvious that, with the exception of the period December-January-February, the seasonal average was nearly constant. The small number of determinations in the group mentioned decreases the significance of the apparently increased value for total serum protein and serum albumin observed.

Toxemic Pregnancy

In the five cases of pre-eclampsia studied, a regrettably small number, the changes in the concentration of serum protein were the greatest observed in the entire series. If it were not that these findings agree so well with those reported by Eufinger,[8] Plass and his associates,[13, 14] Eastman,[6] and Strauss, [16-20] one would be inclined to minimize their significance because of the paucity of cases. The values are recorded in Table III. The values for serum protein, expressed in grams per 100 c.c., shortly before and at delivery were as follows: total protein, average 5.6, range 4.8 to 6.4; albumin, average 3.5, range 3.0 to 4.0; globulin was not calculated since the values did not differ appreciably from those in normal pregnancy. The fall in the value for total protein from the average value obtained in normal nonpregnant women was 19 per cent, the fall in albumin according to the same standard was 33 per cent. The value for total protein was 14 per cent lower, and that for the albumin fraction 12 per cent lower than the lowest average values obtained at any time during normal pregnancy. In these cases the albumin constituted 62 per cent of the total protein, giving an albumin: globulin ratio of 1.65. Case 4, which showed the least lowering of the albumin and total protein, was the mildest of the five cases observed.

Case 1.—The patient was an 18-year-old primipara with a generally contracted pelvis. There was no history of renal disease or any familial history of hypertension. The pregnancy progressed without incident until the eighth lunar month, at which time there were rapid increase in weight, albuminuria, headache, generalized edema, and epigastric pain. While the patient was on a low salt diet in the hospital the visible edema receded and there was no further gain in weight. The blood pressure, however, steadily rose from 120/68 at the onset of her symptoms to 145/100 in the ninth month, at which level it remained until term. After a trial at labor, a normal infant was delivered by low cervical section. The blood pressure dropped within twenty-four hours after delivery to 120/60 and remained there during her stay in the hospital. A mild degree of albuminuria persisted after delivery. The patient has not returned since she left the hospital.

Case 2.—The patient was a 19-year-old primipara with no physical abnormalities. There was no history of renal disease or familial hyper-

TABLE III. CONCENTRATION OF SERUM PROTEIN IN TOXEMIC PREGNANCY

DAYS	SERUM PROTEIN, GM. PER 100 C.C.			REMARKS
	TOTAL	ALBUMIN	GLOBULIN	
				Case 1
6 a.p.	5.2	2.7	2.5	Gained 6 lb. in one wk.; B.P. 120/68
1 a.p.	5.2	2.6	2.6	Headache, generalized edema; B.P. 145/100; low cervical section
3 p.p.	4.8	3.8	1.0	
8 p.p.	7.0	4.9	2.1	Asymptomatic B.P. 120/60
26 p.p.	7.2	4.5	2.7	Asymptomatic B.P. 120/60
				Case 2
19 a.p.	6.7	4.3	2.4	B.P. 150/100; otherwise normal
4 a.p.	5.4	4.3	1.0	B.P. 140/95; albuminuria, grade 3 plus
2 a.p.	5.6	3.4	2.2	Spontaneous labor, premature; B.P. dropped from 160/100 to 120/80 in 24 hr.
3 p.p.	5.3	3.3	2.0	No further pertinent data available
7 p.p.	6.5	3.7	2.8	
11 p.p.	6.1	3.9	2.3	
				Case 3
70 a.p.	6.7	4.2	2.6	
39 a.p.	6.6	4.2	2.4	
17 a.p.	6.0	3.7	2.3	B.P. 152/100; moderate edema; patient hospitalized
10 a.p.	6.1	3.9	2.1	Headache and epigastric pain
2 a.p.	6.1	3.6	2.5	Forceps delivery, B.P. 140/108
1 p.p.	5.7	3.4	2.4	
4 p.p.	6.1	3.9	2.2	B.P. 122/80; asymptomatic
9 p.p.	6.4	4.0	2.4	B.P. 122/80; asymptomatic
				Case 4
161 a.p.	7.3	4.7	2.6	Blood pressure was labile throughout pregnancy. Patient entered hospital 18 days before delivery, with B.P. 138/90 and mild pitting edema. Delivered spontaneously without difficulty. B.P. 175/80 with occasional albuminuria. Clinically, a very mild case of pre-eclampsia
140 a.p.	6.4	4.2	2.3	
119 a.p.	6.4	4.3	2.1	
98 a.p.	6.1	3.6	2.4	
77 a.p.	7.0	4.8	2.2	
56 a.p.	6.5	4.4	2.0	
36 a.p.	6.9	4.0	2.9	
11 a.p.	5.9	3.6	2.4	
3 a.p.	6.1	4.0	2.2	
5 p.p.	6.4	4.2	2.2	
				Case 5
37 a.p.	6.6	4.0	2.6	
30 a.p.	6.8	3.9	2.9	B.P. gradually increased to 126/88
27 a.p.	6.6	3.5	3.1	
21 a.p.	6.4	4.0	2.4	Albuminuria, grade 2 to 3 plus; B.P. 140/90
4 a.p.	5.3	3.1	2.2	Semicomatose, very edematous
1 a.p.	5.5	3.1	2.4	Semicomatose, very edematous
2 p.p.	5.3	3.0	2.3	B.P. 126/86; no albuminuria; symptomatically much better
7 p.p.	6.4	3.4	3.0	
11 p.p.	6.1	3.4	2.7	
17 p.p.	6.8	4.0	2.8	Continued to have albuminuria, grade 1 plus

a.p. = antepartum; p.p. = postpartum.

tension. She was perfectly well until late in the seventh lunar month, at which time a feeling of discomfort developed in the upper part of the abdomen and was accompanied by a mild degree of generalized edema. At this time her blood pressure was 108/68. There was no albuminuria. She was next seen early in the ninth lunar month, at which time her blood pressure had risen to 150/100 and there was moderate albuminuria. She was placed on a salt-free diet; rest in bed was advised and mild sedation was prescribed at home. After two weeks of this regimen, her blood pressure dropped to 130/90 but the other symptoms remained unchanged. During the next week her blood

pressure rose to 140/95. There was no generalized edema, but there was severe albuminuria. She was hospitalized, and after five days, with no change in her symptoms, premature labor occurred spontaneously. At this time the value for the urea nitrogen was 16 mg. per 100 c.c. of blood. The value for the carbon dioxide combining power of the blood plasma was 72 volumes per cent, that for the blood sugar was 132 mg. per 100 c.c. of blood, and the value for the plasma chloride was 480 mg. per 100 c.c. Her blood pressure immediately dropped to 120/80 from 160/100 and remained at that level. Ten days after delivery the value for the urea nitrogen was 20 mg. per 100 c.c. of blood and the urea clearance, maximal, was 73.4 per cent of normal. When she was dismissed from the hospital eighteen days after delivery, slight albuminuria was present. She has not returned.

CASE 3.—The patient was an 18-year-old primipara with no physical abnormalities. There was no history of renal disease or familial hypertension. Her pregnancy progressed normally until early in the ninth lunar month, at which time her blood pressure rose from a normal level to 152/100. Headache and epigastric pain developed and there was a rapid gain in weight accompanied by generalized edema. At no time did she have any great degree of albuminuria. The blood pressure varied between 168/100 and 140/108 after a five-day period of hospitalization on the recommended regimen. Because of the persistent hypertension she was medically stimulated and delivered of a normal infant. Shortly before delivery the value for the urea nitrogen was 11 mg. per 100 c.c. of blood and that for the blood sugar was 68 mg. per 100 c.c. After delivery, the blood pressure dropped to 122/80 and the other symptoms disappeared.

CASE 4.—The patient was a 22-year-old primipara with no physical abnormalities. There was no history of renal disease. Her mother had hypertension. Throughout the entire pregnancy, the blood pressure was labile and varied over a wide range at hourly intervals. She had no albuminuria at any time and no systemic symptoms. She was hospitalized late in the ninth lunar month because of a blood pressure of 138/90. After rest in bed on the recommended regimen for three days, the blood pressure dropped to 120/80, but in view of the previous fluctuations little significance can be attached to this. She signed her own release, against the advice of the physician, after a short period of hospitalization. After a few days, she entered the hospital again in active labor with a blood pressure of 175/80. Albuminuria varied from mild to moderate during the week immediately preceding and following delivery. Shortly before delivery the dilution and concentration test was normal, in spite of the use of a low salt diet, and at the same time the urea clearance was 69 per cent of normal. When she was dismissed from the hospital, her blood pressure was 120/80, and albuminuria was not present.

CASE 5.—The patient was a 30-year-old primipara with no physical abnormalities. There was no history of renal disease or familial hypertension. Throughout pregnancy there was a gradual increase in the diastolic pressure from 120/74 during the third month to 126/88 early in the ninth month. During the eighth and ninth months there was a moderate to severe degree of albuminuria. Her weight increased very rapidly during this period and severe generalized edema developed. At its maximum, shortly before delivery, the blood pressure was 160/96, but rapidly fell to 126/76 after delivery. Labor was induced a little before full term by rupture of the membranes. She continued to have mild albuminuria for two months after delivery, after which the urine became normal.

Serum Protein in Blood of Cord

In so far as is known, no one has studied the concentration of serum protein in maternal blood and blood of the umbilical cord at the time of delivery. Because of the availability of material during the period in which the preceding studies were being made, rather than with the hope of obtaining any significant information, thirteen determinations of this type were made. The maternal blood was obtained by the usual method, immediately after delivery of the child. The blood of the cord was obtained immediately after the second stage of labor. The data are presented in Table IV.

TABLE IV. CONCENTRATION OF SERUM PROTEIN OF MATERNAL BLOOD AND BLOOD OF CORD AT THE TIME OF DELIVERY

CASE	SERUM PROTEIN, GM. PER 100 C.C.					
	MATERNAL BLOOD			BLOOD OF CORD		
	TOTAL	ALBUMIN	GLOBULIN	TOTAL	ALBUMIN	GLOBULIN
1	6.6	4.4	2.2	6.6	4.5	2.1
2	7.2	4.7	2.5	7.0	4.7	2.3
3	6.4	4.1	2.3	6.3	4.2	2.1
4	6.6	4.1	2.5	6.4	4.4	2.0
5	6.8	4.4	2.5	6.1	4.1	2.0
6	6.2	4.4	1.8	5.5	3.8	1.7
7	6.3	4.3	2.0	6.0	4.3	1.7
8	7.1	3.9	3.2	6.3	3.6	2.7
9	6.9	3.9	3.0	6.5	3.9	2.6
10	6.4	3.9	2.5	5.8	3.9	1.9
11	6.0	4.3	1.7	6.5	4.6	1.9
12	5.8	3.8	2.0	6.0	4.3	1.7
13	6.6	4.2	2.4	6.6	4.3	2.3
Average	6.5	4.2	2.3	6.3	4.2	2.1

The individual determinations showed some variation, usually an increase in total protein and globulin in the maternal blood. The values for albumin were nearly the same in both maternal and cord blood, and when the series was averaged they were exactly the same. The occurrence of a lower level of globulin in most specimens of blood of the cord may be ascribed to the known deficiency of antibodies in the newborn infant. The most remarkable feature of the whole series is the close correlation between the albumin in the fetal and maternal blood, indicating that a delicate osmotic balance is maintained across the placenta.

Comment

Within the past few years it has been shown that the liver is the principal organ in the body concerned with the manufacture of serum albumin. The evidence supporting this has been thoroughly reviewed by Whipple and Robscheit-Robbins.[26] Numerous investigators, including Kaufmann,[27, 28] Botella-Llusiá,[29] Neuweiler,[30, 31] Cross,[32] Hirsheimer,[33, 34] Sullivan and his associates,[35] and Hofbauer[36] have studied the function of the liver with a variety of tests during pregnancy. They all found that the ability of the liver to synthesize or dispose of various substances is markedly impaired during the latter part of pregnancy, and even more so in toxemic pregnancy. The curve of liver function during pregnancy roughly follows that of the serum albumin, both being depressed during the latter months. Hofbauer, after an extensive study of the changes in the blood during pregnancy, concluded: "The latent liver damage of pregnancy is directly related to the known changes in the blood: In-

crease in the sedimentation rate, changes in the acid-base relationship, changes in colloid stability, increase of globulin, decrease of surface tension, hemoclastic crises." It may develop that the hormonal changes associated with pre-eclampsia are due to an impaired metabolism of these substances in the liver.

It is the opinion of an increasing number of investigators that many, if not all, of the manifestations of true eclamptogenic toxemia may be explained on the basis of a disturbance in protein metabolism. Obviously there must be predisposing factors present in the maternal organism and its environment or eclampsia would be more prevalent than it is. Some of these factors may be as follows:

1. Multiple pregnancy, polyhydramnios, or hydatid mole, causing a rapid increase of intra-abdominal pressure and interfering with the portal circulation and absorption of metabolites from the intestine.

2. A diet deficient in protein, unable to supply the needs of both the mother and the fetus.

3. Restriction of food and fluid plus parenteral administration of salt solution, as advocated in certain therapeutic regimens.

4. Anatomic abnormalities of the abdominal viscera or bony pelvis, disturbing the abdominal circulation as in *1*.

Summary and Conclusions

Two hundred fifty-one determinations of the serum protein of seventy-nine normal pregnant women and thirty-nine determinations on five pre-eclamptic women were made. The average value for serum globulin remains almost constant throughout normal and toxemic pregnancies. During the normal pregnancy the average value for the total protein tends to fall from the nonpregnant level to a minimum during the eighth to ninth month and to rise rapidly to normal after delivery. At its lowest point this represents a decrease of 7.1 per cent from the nonpregnant average. This decrease in the concentration of total protein is confined primarily to the albumin fraction. The albumin decreased from a nonpregnant average value of 4.9, to 4.0 Gm. per 100 c.c., a fall of 14 per cent. The average value for total protein in pre-eclampsia was 14 per cent below that of normal women in the same stage of pregnancy. This decrease in total protein is confined to the albumin fraction. It was 12 per cent lower than the lowest average value obtained at any time during normal pregnancy, and 33 per cent lower than the average for normal nonpregnant women. The probable dependency of these changes on known alterations of the function of the liver during pregnancy has been considered. A total of fifteen determinations of the serum protein in simultaneously drawn maternal blood and blood of the cord was made. The albumin content of maternal serum and serum of the cord is nearly identical; a slight difference is noted in the globulin fraction.

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THE TREATMENT OF FUNCTIONAL DYSMENORRHEA WITH PREGNENINOLONE

Floyd E. Harding, M.D., Los Angeles, Calif.
(From the Department of Endocrinology, Ross-Loos Medical Group)

FUNCTIONAL or primary dysmenorrhea is a very puzzling condition that frequently does not respond to therapy. It results in much suffering and loss of time by the patient. A simple, harmless, and effective method of treatment is, therefore, greatly needed. With this in mind, patients have been observed following the oral use of pregneninolone.

Pregneninolone, synthesized in 1938,[14, 36] is a crystalline substance that differs only slightly from progesterone. There is the substitution of OH for H in the 17-position and subtraction of H_2O from the side chain. Hence, it is sometimes called anhydroxy-oxyprogesterone and it has been shown to have essentially the same clinical effect as progesterone. There is, however, at least one great difference—it is effective when administered orally.

When progesterone became available for clinical use, it replaced the corpus luteum preparations. The early corpus luteum extracts were ineffective because they contained no appreciable amount of active substance.

Although progesterone was quite generally used from 1935 to 1940, its therapeutic indications were rather obscure. Clinicians, who had

observed the effects of progesterone on women with uterine pain, reported that some of the patients were free from pain when it had been given.[5, 6] Thus, progesterone seemed to be definitely indicated for dysmenorrhea.[18-20, 25]

Following this general observation, gynecologists attempted to find a type of dysmenorrhea for which progesterone would be specific. This work failed in its purpose, but some interesting facts were established as a result of this and other research. First, progesterone changed the endometrium from an estrogenic (proliferative) to a progestational (secretory) type in human beings as well as in animals.[2, 10] Second, uterine biopsy showed that most patients with dysmenorrhea bled from a progestational endometrium.[3] When abnormality occurred, however, underdevelopment of the endometrium was more common than overdevelopment.[23, 24] Third, there was no agreement as to whether dysmenorrhea patients with anovulatory menstruation were benefited more by progesterone therapy than dysmenorrhea patients with menstruation following ovulation. Also, it was claimed that patients had no pain when anovulatory menstruation was produced with large doses of estrogens.[9, 12, 21] Fourth, urine assays for pregnandiol, a substance derived from progesterone, would be of no value in dysmenorrhea even though they might be a guide to diagnosis of anovulatory menstruation.[3, 4, 8]

How is the pain relieved with progesterone? Animal experiments were made, showing that progesterone inhibits uterine contractions which ordinarily follow injections of pituitrin. Based on this fact and the observed clinical action of the corpus luteum hormone in preventing spontaneous abortion, progesterone was considered a uterine inhibitor, that is, an antagonist of estrogen.[16-18, 26]

This mechanism of relief of pain has been questioned, however, and other theories, too numerous to mention here, have been suggested.[1, 11, 13, 22, 28, 31, 32] Since the cause of pain may have nothing to do with uterine contractions, settling the dispute as to whether progesterone increases or decreases them is of little clinical aid. It is known, however, that uterine cramps increase in the premenstrual period when estrogen and progesterone are increased, but during pregnancy, when they are greatly increased, the uterine cramps are inhibited.

It cannot be said positively that functional dysmenorrhea is caused by endocrine disease, but endocrine function is at least a contributing factor. Treatment with estrogen,[9, 12, 29, 30] progesterone,[20, 25, 33] and testosterone[27] changes the type and amount of menstruation, length of menstrual cycle, and amount of menstrual pain.

The action of pregneninolone is very similar to that of progesterone.[15, 37] It has been suggested, however, that pregneninolone may be more effective for the relief of dysmenorrhea than progesterone.[3]

The papers previously published on the use of pregneninolone for functional dysmenorrhea have shown it to be beneficial.[3, 7, 34, 35]

Patients Studied

Of the eighty-two patients treated, thirty-one were single and fifty-one married. They were in the following age groups:

Age	11-20	21-30	31-40	41-50	51-60
No. of patients	17	33	25	6	1

Fifty-five women, twenty-four of whom were married, had no children. Twenty-seven women had children. There were forty-two children in all. Menstruation began at the following ages:

Age	10	11	12	13	14	15	16	17
No. of patients	4	16	29	17	10	3	2	1

The patients in this group were more neurotic than an equal number of individuals picked at random. The dysmenorrhea was of long standing in the great majority of patients, the date of onset ranging from the beginning of puberty to five years before the initiation of the present treatment. Pelvic examinations were essentially negative, and all cases were diagnosed as functional dysmenorrhea. The patients were referred to the endocrine department by other physicians. Nearly all the patients had been given one or more types of medical or surgical treatment. Most of them had had endocrine injections. None of the patients were satisfactorily relieved by nonnarcotic analgesics. It was believed that previous treatment would largely rule out psychological response to the treatment with pregneninolone.

Method of Treatment

The pregneninolone* was administered orally in 5 mg. tablets. The daily dose was 5 mg. in sixty-nine patients, 10 mg. in twelve patients, and 15 mg. in one patient.

Days during which the tablets were given	No. of patients
14th day of cycle until menstruation started	5
18th day of cycle until menstruation started	52
20th day of cycle until menstruation started	1
21st day of cycle until menstruation started	4
23rd day of cycle until menstruation started	1
24th day of cycle until menstruation started	1
18th day of cycle until pain had lessened	18

The days were counted from the first day of the last menstruation.

No other treatment for dysmenorrhea was administered during the treatment with pregneninolone. Tablets for pain were not prescribed, and the patient was instructed to report for advice if pain occurred.

Results With Pregneninolone

Eighty-two patients with dysmenorrhea were treated with pregneninolone tablets. There was 50 per cent or more improvement in sixty patients and less than 50 per cent improvement in twenty-two patients. Thus, the treatment was considered satisfactory for 73 per cent of the patients. Six patients were classified as worse because there was more pain during the months treated. Two patients became pregnant and did not menstruate after taking the tablets. Table I shows the average percentage of improvement during the months treated. This percentage was based on the amount of pain estimated by the patient and her relatives, the request for pain-relieving therapy and the amount required, the length of time the patient was bedridden or unable to work, her general appearance, etc.

TABLE I. PREGNENINOLONE TREATMENT OF FUNCTIONAL DYSMENORRHEA

Improvement in %	Worse	0	25	35	50	65	75	85	90	100	Pregnant
No. of patients	6	11	3	2	11	4	15	4	6	18	2

*The pregneninolone (Pranone) was obtained from the Schering Corporation, Bloomfield, New Jersey.

The prevention of pain was considered to be temporary as the patients were usually only benefited in the month that medication was taken. A follow-up of these patients, however, showed that occasionally the pain did not return for two or three months after the tablets were discontinued. A few patients were seen six months to a year later, and the dysmenorrhea had not returned. Some patients also stated that while the pain became worse when treatment was stopped, it did not become as bad as it was before treatment had been given. Frequently, the duration of pain was cut down one, two, or three days. There was some variation in the amount of pain from month to month while taking the tablets, and a few patients claimed that the pain was present some months and not others. In these patients the pain might occur the first month or any succeeding month.

Other severe symptoms associated with dysmenorrhea were prevented in the following instances: vomiting, 5; nausea, 6; diarrhea, 1; and dizziness, 2. One patient had relief of vomiting without relief of pain. Many of the other patients had mild gastrointestinal symptoms which were relieved if the pain was relieved, and vice versa. There was no relief from severe nausea in two patients. Premenstrual tension was relieved in a few patients.

Most of the patients felt "no different" while they were taking the tablets, but a few felt better and the effect appeared to be similar to that observed with the use of stimulants. This improvement was different from the "tonic effect" noted with the use of estrogens. It was described by Hamblen and his associates[4] as a "mild euphoria."

Periodic pain frequently was deterimental to the physical and mental well-being of these patients. When the pain was prevented by the taking of a few tablets, the patient experienced a sense of security and confidence, and no longer feared that the condition might become worse or the pain and other symptoms unbearable. In subsequent months the nervousness subsided; some gained weight; and others looked better, had a better color, and appeared more rested.

Effects Upon Menstruation

Before treatment the menstruation was essentially regular in thirty-nine patients and irregular in forty-one patients. Thirty-one patients were usually late, twenty-seven on time, thirteen early, and nine mixed (late and early). Data were not obtained from two patients.

The figures in Table II show that with the method used there was a tendency for pregneninolone to cause earlier menstruation except when menstruation was quite early before treatment. There was no change in the amount of flow in three-fourths of the patients regardless of whether the pretreatment menstruation was heavy, scanty, or normal; but when a change occurred, the heavy periods usually became lighter, and vice versa. Two patients with excessive menstruation, however, bled very much more heavily following treatment. There was no change in the duration of flow in about three-fourths of the patients regardless of type, but when a change did occur the longer periods became shorter and vice versa. The menstrual changes that occurred with treatment were usually an improvement except for the normal twenty-seven- or twenty-eight-day cycle that was shortened.

Where early menstruation had been caused in previous months by the tablets, starting the use of preneninolone later in the cycle, on the twentieth to the twenty-fourth day, prevented the onset of menstruation before the twenty-eighth day.

It must be kept in mind that small doses were used in this study. Larger doses would have produced greater changes in menstruation and in some instances would have caused a different response. Giving the tablets during other parts of the cycle would also have made a difference.

TABLE II. MENSTRUAL CHANGES AFTER TREATMENT

	NO. OF PATIENTS
1. *Change of Cycle*	
Earlier menstruation (before treatment 30 had been late, 9 on time, 3 mixed, and 1 early)	43
Later menstruation (before treatment 8 had been early, 4 on time, and 2 mixed)	14
Same length of cycle (before treatment 14 had been on time, 4 early, 4 mixed, and 1 late)	23
2. *Amount of Flow*	
Less in amount (before treatment 7 were excessive and 2 normal)	9
More in amount (before treatment 6 were scanty, 2 excessive, and 1 normal)	9
Same amount	62
3. *Duration of Flow*	
Shorter duration (these were seven or more days long before treatment)	11
Longer duration (before treatment 3 patients had one- or two-day periods and 6 had three-day periods)	13
Same duration	56

The length of cycle and duration of each period were considered to be accurate because each patient kept this record on a card* containing one year of twenty-eight-day cycles. Estimation of the amount of flow, of course, was dependent on the patient's judgment, and was therefore less accurate.

Reactions

The use of pregneninolone for seven to ten days before menstruation was considered harmless with the dosage used. There was no evidence of pituitary inhibition. It apparently had no effect upon the ovary, but there was a definite effect upon the uterus.

Two patients felt "keyed up" from the tablets. Nausea and vomiting occurred at menstruation in one patient who never had had these symptoms with her periods. There were no other reactions.

Results With Progesterone Injections

Twenty patients were given injections of progesterone in doses of 5 mg. to 15 mg. during the time that the patient complained of severe pain. The results of this treatment were disappointing, and as very little relief was obtained, this method was discontinued.

Later, twenty-two patients were given progesterone injections between menstrual periods. The dose ranged from 1 mg. to 5 mg. Eleven patients were treated all month while the other eleven were treated during the last two weeks of the cycle. Three patients were treated daily, but the others were treated two or three times a week. The following results were obtained: no better, 9; slight improvement, 2; 50 per cent improvement or better, 4; and 100 per cent improvement, 5. Four patients became pregnant during treatment, two the first month and two after a few months. These last two had just as severe dysmenorrhea during treatment as before. One pregnant patient had been previously considered sterile. A patient who always menstruated regularly every twenty-eight days menstruated every fourteen days for four periods while treatment was given all month. With the method used,

*Supplied through the courtesy of Mead Johnson & Co., Evansville, Ind.

this treatment was not as beneficial as the oral use of pregneninolone. Therefore, these injections were discontinued because they caused too much inconvenience and were too expensive for a treatment usually giving temporary relief.

The older case records between 1930 and 1935 were reviewed, and it was found that forty-seven patients had been treated with injections of corpus luteum twice a week throughout the menstrual cycle. Results were generally poor with this treatment. It was believed that corpus luteum injections with the material used were without value because they contained negligible quantities of progestins, and that any improvement was due to other factors. When improvement was noticed, it was usually found in milder cases and those of short duration without previous treatment. There was rarely any improvement in the patient whose pain began with the first menstrual period of puberty and in the patient where numerous other methods of treatment had been used without success. This latter type of patient with long-standing dysmenorrhea, however, was frequently benefited with pregneninolone.

Discussion

There were many advantages with pregneninolone therapy. The oral method saved the time of both the patient and the doctor. Numerous trips to the office were required for injections of progesterone but were unnecessary when tablets of pregneninolone were given. This decrease in office calls was especially important during the war because of lack of transportation. Local reactions from injections were eliminated by oral treatment. Most of the patients would not come for daily injections of progesterone, whereas, there was no objection to taking the tablets daily. The cost of daily injections was frequently prohibitive or impractical; but when the tablets were purchased in quantities of 100 or more, the cost of six to ten days' treatment was much less. Absenteeism due to dysmenorrhea was cut one day to two weeks. As a large percentage of these patients were employed, this amounted to a considerable saving of money from wages otherwise lost. Also, keeping the patient at work cut down loss of production in war plants and was responsible for more efficient service elsewhere. When successful, this method was certainly to be preferred to surgery or other more complicated and expensive measures.

There were no disadvantages except that improvement was usually temporary and did not occur in all patients. In rare instances menorrhagia was increased.

The effective dose in this series was only 5 mg. per day for ten days prior to menstruation, whereas Soule[7] used 60 mg. per day for five days prior to menstruation. Greenblatt and his associates[3] found that 5 mg. to 10 mg. for the twelve days before menstruation was effective. It was surprising that a therapeutic result was obtained with such small doses. Results with injection therapy would make it seem that larger doses were needed orally.

To be successful, treatment had to be given in the premenstrual period. Maintaining a higher blood level of hormone by injections after the pain began was without benefit. Pregneninolone was given until the bleeding occurred. Menstruation, therefore, started during treatment rather than after withdrawal.

The pain of functional dysmenorrhea is probably not caused by uterine contractions. A more likely explanation would be secretory or

vascular congestion, possibly with muscular tetany, causing a pressure or ache with normal uterine contractions making the pain cramplike in character at times. Relief is usually obtained when patients begin to menstruate freely and some of the endometrium has sloughed off. As dysmenorrhea frequently begins a day or two before menstruation, it could not be caused by obstruction or clots. The abnomal sensation comes from the uterus as it can be stopped by cutting the nerves from this organ. What causes the condition is unknown. Glandular function is normal in many cases as near as it is possible to tell with present methods of diagnosis. However, there is no doubt that large doses of estrogens inhibiting ovulation, testosterone, or pregneninolone change the pain-producing mechanism in such a way as frequently to prevent the pain. They produce changes in the endometrium and changes in vasoconstriction. Of these three, pregneninolone seems preferable, as the use of the other two is nonphysiologic.

Occasionally, other physiologic endocrine therapy is indicated. Hypothyroid patients respond to thyroid therapy. The underweight patient is improved with a diet and insulin. The small undeveloped uterus with hypoplastic endometrium improves with small or moderate doses of estrogens. This study, however, was limited to the effect of products causing progestational changes and did not include cases treated with other endocrine preparations.

Summary

Eighty-two patients with functional dysmenorrhea were treated by giving pregneninolone orally. There was satisfactory improvement (50 per cent or better) in sixty patients. It was interesting to note that the small 5 mg. dose was effective. Nausea and vomiting did not occur when the pain was prevented. The improvement was limited mainly to the month treated. There was a tendency for the treatment to cause earlier menstruation. This method of treatment had many advantages, such as simplicity, harmlessness, and low cost. There was an important saving in the time of both patient and physician. In order for the treatment to be successful, it had to be given daily for seven to ten days before menstruation. When it was administered during menstruation, there was little benefit.

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947 West Eighth Street

THE POSSIBLE ROLE OF BACTERIAL SYNERGISM IN PUERPERAL INFECTIONS DUE TO ANAEROBIC STREPTOCOCCI

Seymour R. Steinhorn, B.S., M.S., Chicago, Ill.

(From the Department of Bacteriology, Northwestern University Medical School)

THE present report represents the results of an investigation of two points of interest concerning the role of anaerobic streptococci in puerperal infections. The first of these is the incidence of various bacteria in the uterus in infections following childbirth and abortion. Particular attention was directed to the relative frequency with which anaerobic streptococci are recovered as compared with hemolytic streptococci. Other studies of this aspect have yielded conflicting results. Secondly, what is the causal relationship of anaerobic streptococci to these infections? Investigation of this factor was deemed advisable since their role has been questioned on the basis of the absence of virulence for laboratory animals in previous experiments and their frequent occurrence in the vagina of normal women.

The association of anaerobic streptococci with puerperal infection has been recognized since the descriptions by Menge and Kroenig[16] in 1899 and Natvig[17] in 1905 of their presence in the lochia of women affected with this disease. Schottmüller[20] recovered them from the blood in similar cases. Schwarz and Dieckmann[21] noted that these organisms were isolated from 64.3 per cent of their cases. In Colebrook's[6] experience anaerobic streptococci alone or in association with other organisms caused two-thirds of the septicemias and one-third were due to hemolytic streptococci. Brown[4] reported the occurrence of anaerobic streptococci in 84.1 per cent of 246 cases. Somewhat different results were obtained by Harris and Brown[9] who recovered anaerobic and hemolytic streptococci with almost equal frequency. Divergent observations were made by Fitzgibbon and Bigger[8] who recovered hemolytic streptococci from 56 per cent of 51 patients and anaerobic streptococci from 2 per cent. In the experience of Rivett, et al.,[19] there was a 39 per cent incidence of hemolytic streptococci while anaerobic streptococci occurred in 29.4 per cent of the cases.

The concept of bacterial synergism has been increasingly studied since Pasteur's[18] observation that certain aerobes facilitated the growth of anaerobes by consuming the available oxygen. The term "bacterial synergism" was first employed, however, by Kämmerer[11] in 1923. Other investigations[5, 10, 22, 23] indicate that this phenomenon occurs in many bacterial associations. The work of Meleney is closely related to the material of the present investigation. He[13] showed that a nonhemolytic diphtheroid could augment the hemolysis of a double-zoned *Staphylococcus aureus*. Later he[14] vividly demonstrated in vivo synergism with a microaerophilic nonhemolytic streptococcus and a faintly hemolytic *Staphylococcus aureus*. Meleney and his associates[15] also reported similar results with other organisms. The postoperative synergistic gangrene of the abdominal wall which he described is frequently referred to as "Meleney's Gangrene."

The investigations of the pathogenicity of anaerobic streptococci have yielded almost uniformly negative results. Veillon[25] needed considerable amounts of his cultures to produce only subcutaneous abscesses in animals. Natvig[17] and Schottmüller[20] failed to demonstrate any pathogenic activity. More latterly, McDonald, et al.,[12] were unable to produce lesions in animals by employing a variety of routes of injection of pure cultures of their twenty-three strains. They concluded that all their strains were practically nonvirulent for laboratory animals.

Materials and Methods

1. *Clinical Material.*—The 37 patients studied in this investigation were those with a temperature of 100.4° F., or above, which was sustained for twenty-four hours or more or occurred on separate occasions on two successive days within ten days of the birth or abortion. A clinical course satisfying these requirements was considered febrile. Most of the cases were diagnosed endometritis.

2. *Collection of Specimens.*—The vulva was carefully cleansed, a sterile speculum was inserted, and the orifice of the cervical canal was wiped with sterile gauze. Lochia was aspirated from the uterine cavity by means of a pipette made of a piece of glass tubing with a rubber bulb on one end. The pipette was in a large test tube, which was plugged with cotton and autoclaved as a unit prior to use.

3. *Media and Cultural Methods.*—Glucose infusion broth and thioglycollate broth[2] were used routinely for primary cultivation. Tubes of these were available at the bedside, and, immediately upon collection of the lochia, half of the total volume obtained was introduced into a tube of each of these media. This material was brought to the laboratory within two hours. Several loopfuls from the thioglycollate broth were streaked onto thioglycollate agar in the anaerobic dish described by Brewer.[3] Material from the glucose broth was similarly plated onto two blood agar plates, one for aerobic, the other for anaerobic cultivation. These plates and the tubes inoculated at the bedside were incubated at 37° C. The aerobic blood agar plates and the glucose broth tubes were observed for growth at the end of twenty-four hours. Smears were made and any growth was subcultured on blood agar plates for pure culture study. Growth occurring in the thioglycollate broth was transferred to thioglycollate agar in the Brewer dish and to blood agar plates for anaerobic cultivation. The anaerobic jars were not opened before forty-eight hours of incubation. Any growth at the time of observation was transferred to thioglycollate agar in the Brewer dish and to two plates of blood agar for aerobic cultivation to determine the presence of facultative anaerobes or microaerophilic organisms.

4. *Pathogenicity of Anaerobic Streptococci.*—Pure cultures of anaerobic streptococci were transferred to blood agar plates and incubated anaerobically. These were observed daily for the first indication of growth, which usually required two to six days. At this time approximately one loopful of the surface growth was suspended in 3 c.c. of 0.85 per cent NaCl and mixed thoroughly. One cubic centimeter of this suspension was injected subcutaneously beneath the abdominal skin of each of three white mice. The animals were observed daily for evidence of infection. These tests were used as controls for the tests of synergism.

5. *Tests of Synergism in Vivo.*—The same suspensions employed in determining the pathogenicity of the anaerobic streptococci were used. Doses of 0.5 c.c. of these suspensions combined with 0.1 c.c. of suspensions of *Staphylococcus albus* (SAL-4), similarly prepared, were injected beneath the abdominal skin of each of three white mice of approximately equal size. Two additional mice were used as controls for the staphylococcus and were injected by the same route with 0.5 c.c. of the same suspension of staphylococcus alone. SAL-4 is the strain of *Staphylococcus albus* isolated from one case. Strains of staphylococci from all other

cases were tested in the same manner, as were three other strains isolated, respectively, from the normal human skin, from the normal human throat and from the air of the laboratory.

6. *Tests of Synergism in Vitro.*—Blood agar plates were streaked with parallel rows of anaerobic streptococci separated by a space about 1 cm. wide. Midway between two adjacent streaks a streak of a staphylococcus culture was made. The plates were incubated anaerobically and were observed daily for the appearance of growth.

Results

The percentage incidence of the various organisms is given in Table I. The predominating species were anaerobic streptococcus, hemolytic streptococcus, *Staphylococcus albus*, and *Bacterium coli*. Pure cultures of anaerobic streptococci were found in fourteen cases (37.8 per cent). The over-all occurrence of anaerobic streptococci both in pure culture and with other organisms was 45.9 per cent. Pure cultures of hemolytic streptococci were isolated from three cases (8.1 per cent) and in association with other organisms from four cases (10.8 per cent). In all, hemolytic streptococci were present in 18.9 per cent of all cases. *Staphylococcus albus* was recovered in pure culture and with other organisms in 29.7 per cent of the cases. *Bacterium coli* was identified in pure and mixed culture in 21.6 per cent of the cases.

None of the strains of anaerobic streptococci could be grown in the presence of oxygen even after long periods of artificial cultivation. Most of them, moreover, became nonviable after several months and none survived more than fourteen months.

TABLE I. THE INCIDENCE OF VARIOUS ORGANISMS IN THIRTY-SEVEN CASES OF PUERPERAL INFECTION

ORGANISM	NUMBER OF CASES	PERCENTAGE OCCURRENCE
Anaerobic streptococci alone	14	37.8
Anaerobic streptococci and others	3	8.1
Hemolytic streptococci alone	3	8.1
Hemolytic streptococci and others	4	10.8
Staphylococcus albus alone	4	10.8
Staphylococcus albus and others	7	18.9
Bacterium coli alone	3	8.1
Bacterium coli and others	5	13.5
Streptococcus viridans and others	2	5.4
Hemophilus ducreyi (?) and others	1	2.7
Streptococcus anhemolyticus and others	1	2.7
Diphtheroids	4	10.8

TABLE II. PATHOGENICITY AND BLOOD PLATE HEMOLYSIS RESULTING FROM THE ASSOCIATION OF SEVENTEEN STRAINS OF ANAEROBIC STREPTOCOCCI WITH A STRAIN OF STAPHYLOCOCCUS ALBUS (SAL-4)

STRAIN NUMBER	ACTION ON BLOOD AGAR	MICE WITH BOTH ORGANISMS			CONTROLS PURE CULTURES OF ANAEROBIC STREPTOCOCCI			CONTROLS PURE CULTURES OF STAPH. ALBUS (SAL-4)	
1	beta	+++	+++ 19	+++	0	0	0	0	0
3	beta	++	++	+++	0	0	0	0	0
4	beta	++	++	++	0	0	0	?	?
6	gamma	+	+	++	0	0	0	0	0
8	gamma	+	++	+	0	0	0	0	0
15	beta	+++	+++	+	0	0	0	0	0
16	beta	+++	+++ 17	+++ 15	0	0	0	?	0
17	beta	++	++	+++	0	0	0	0	0
18	beta	+++	++	+++	0	0	0	0	0
21	gamma	++	++	++	0	0	0	?	?
22	beta	+++ 7	+++	+++ 18	0	?	?	0	0
23	beta	+++	++	++	0	0	0	0	0
25	beta	+++	++	+	0	0	0	0	0
32	gamma	++	+++ 15	++	0	0	0	0	0
33	gamma	+	+	+	0	0	0	0	0
34	beta	++	+	+	0	0	0	0	0
37	beta	++	++	+++	0	0	0	0	0

? = slight reaction—swelling and erythema.
Numbers refer to days on which mice died after injection.
+ signs = relative degree of ulceration and necrosis.

The most striking results were obtained in observing the potentiating power of a strain of nonhemolytic *Staphylococcus albus* (SAL-4) on the hemolytic abilities and pathogenicity of the anaerobic streptococci (Table II). Whereas only one strain (5.9 per cent) was originally found to exhibit any hemolysis, and this was slight, twelve strains (70.5 per cent) manifested true beta hemolysis when grown in association with this strain of staphylococcus. The staphylococcus (SAL-4), when growing with the anaerobic streptococci, at times produced some hemolysis itself, but when this occurred it was slight.

Of even more direct interest were the results obtained in studying the in vivo effect of the staphylococcus (SAL-4) on the anaerobic streptococci. Pure cultures of anaerobic streptococci injected subcutaneously beneath the abdominal skin of mice produced a lesion in only one of seventeen cases and this was only a little swelling. Suspensions of the staphylococcus (SAL-4) produced only a slightly raised erythematous area in five mice which completely resolved in three to five days. When, however, one-half the amount of the same suspensions of anaerobic streptococci was mixed with one-fifth the amount of the suspension of the staphylococcus (SAL-4) and injected subcutaneously, marked ulceration and necrosis of the abdominal wall resulted, and in six instances the animals died (Table II). All other strains of *Staphylococcus albus* gave negative results, that is, no synergism could be detected either in vitro or in vivo.

Discussion

The occurrence of anaerobic streptococci in the majority of postpartum and postabortal infections as observed by others[4, 6, 21] was reaffirmed in this investigation.

The contradictory results of other series may be explained by careful analysis of these reports. The citations by Fitzgibbon and Bigger[8] of a 56 per cent incidence of hemolytic streptococci and that of Rivett, et al.,[19] of a 39 per cent incidence of hemolytic streptococci and a 29.4 per cent incidence of anaerobic streptococci convey the impression that most of these infections are due to hemolytic streptococci. Furthermore, certain present-day textbooks of obstetrics give the same information. Actually, the figures of the studies referred to do not represent the averages of all cases but, rather, of the severely ill. It is generally conceded that most of the fulminating and fatal infections are caused by hemolytic streptococci, but that the majority of all cases of puerperal infection is due to these organisms is not supported by the available evidence. This is important because, while the sulfonamides have a definite therapeutic value in combating hemolytic streptococcic infections, they are practically useless against anaerobic streptococci, and any toxic drug manifestations may be detrimental to the recovery of patients infected with the latter organisms.

A discussion of the significance of anaerobic streptococci in puerperal infections recalls the correspondence of Armstrong and Burt-White[1] and Colebrook.[7] The former questioned Colebrook's interpretations of his studies of puerperal infections and asked: "May it not be that the provocative factor is intrauterine manipulation, or trauma, and that the infection by various endogenous streptococci and other organisms is a sequel?" To this Colebrook answered: "Since I have seen seven women die from these infections and as many more in grave danger, during the past two years, I am inclined to attach considerable importance to them." It is true that these organisms are a part of the normal vaginal flora in a large number of women[24, 26] but, nevertheless, their frequent presence in the infected uterus in pure culture indicates that they may participate in the actual invasion of tissue instead of being mere saprophytes. The aciduric bacilli are almost universal in their occurrence in the normal vagina, yet, they are conspicuous by their absence from the genital

tract of puerperal women. This indicates that while these bacilli are simple saprophytes and are unable to meet the defenses of the host, whether this be a specific bactericidal one or a pH shift, the anaerobic streptococci manifest some degree of invasiveness or, at least, a greater resistance than the vaginal bacilli. It is possible that the failure to demonstrate this invasiveness with pure cultures in experimental animals is due to species resistance and that, if a susceptible animal were found, this property might be elicited.

The results of the present study have elucidated, to some extent, the problem of the virulence of the anaerobic streptococci. It has been shown that, in association with a particular strain of a staphylococcus, these organisms may display marked virulence for mice and extensive hemolysis of blood agar, whereas either organism alone was incapable of producing these changes. The patient from whom this strain of staphylococcus was isolated also harbored an anaerobic streptococcus. The clinical course in this case was extremely stormy and ended fatally, the only death in the group. On the basis of the enhanced growth on the artificial media and the assumption of hemolytic activities, the anaerobic streptococci seemed to have derived all the benefit from the association; the staphylococcus never appeared to gain anything from the in vitro relationship.

In addition to the in vitro action of bacterial association, Meleney[14] demonstrated that a strain of nonhemolytic microaerophilic streptococcus and a faintly hemolytic *Staphylococcus aureus* from a case of progressive gangrene of the abdominal wall produced gangrene in the skin of dogs and guinea pigs, when injected in amounts half as large as those of pure cultures which failed to evoke the lesion. The experimental results of the present study are in close accord with those of Meleney and his associates. The significance of the finding that such a synergistic process may be at work in certain cases of puerperal infection with anaerobic streptococci may have far-reaching implications. It has been shown that the type of organisms which many years ago was thought to be avirulent by numerous workers and more latterly by McDonald, et al.,[12] may, in fact, attain considerable virulence in infectious processes when associated with other organisms. The strain of staphylococcus used in this study was found purely by chance. This, nevertheless, illustrates the possibility that other potentiating strains, of other organisms as well, may exist.

In severe infections where an anaerobic streptococcus is recovered in pure culture, it is possible that initially another organism, the synergist, was also present but that it has been removed from the field by the defenses of the host, due, possibly, to a greater susceptibilty of the synergist. It is also possible that in some instances the anaerobic streptococcus alone may be the cause of a serious postpartum infection. This may be explained on the basis of a lowered resistance of the patient or to some enhancement of the virulence of the organism by means other than synergistic.

In the past, but fleeting mention was made of "symbiosis" and related processes in connection with puerperal infections. With the demonstration that such a phenomenon actually occurs with these organisms in mice, further attention could profitably be focused along these lines of investigation.

Summary

1. The virulence of anaerobic streptococci is markedly potentiated by their association with a strain of *Staphylococcus albus* so that such mixtures are highly invasive for white mice.

2. Anaerobic streptococci represent the majority of bacteria isolated from the uteri of thirty-seven women with puerperal infection.

3. It is suggested that bacterial synergism may account for some cases of severe puerperal infection with anaerobic streptococci.

The author wishes to acknowledge the privileges accorded him by the Obstetrical Staff of Cook County Hospital.

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303 East Chicago Avenue

EXPERIENCE WITH CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS AT THE UNIVERSITY OF MICHIGAN HOSPITAL

Report of 250 Consecutive Cases

George J. Andros, M.D., and Charles W. Henderson, M.D.,
Ann Arbor, Mich.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

CONTINUOUS caudal analgesia is being used at the University of Michigan Maternity Hospital for relief of pain during labor and delivery. At this time it is the procedure of choice in properly selected patients who do not present contraindications.

This preliminary report summarizes the results in the first 250 consecutive cases delivered via the vaginal route in which the caudal procedure was used. It does not include cesarean sections or gynecologic surgical cases where this form of anesthesia was employed. The 250 cases represent 79.7 per cent of all patients delivered vaginally during the period of time covered by this report.

The technique used is that of Hingson and Edwards, first described in 1942.[1] A malleable steel needle is inserted into the sacral canal through the caudal hiatus, and intermittent injections of 1.5 per cent Metycaine in Ringer's solution are carried out by means of a closed system incorporating a feeding syringe and a receptacle for the anesthetic agent.

The anesthetic agent acts extradurally in the sacral canal to obliterate motor and sensory impulses to and from the perineum and lower vagina (pudendal nerves), cervix and upper vagina (sacral parasympathetic fibers). Anesthesia and muscular relaxation of these structures are accomplished.

With injection of adequate amounts into the sacral canal, the height of the fluid agent in the posterior and lateral peridural space and the subsequent analgesic effect can be raised to the eleventh and twelfth thoracic segments—where thoracolumbar sympathetic fibers bearing pain impulses from the contracting uterine muscle enter the cord with the dorsal nerve roots.

Motor stimuli to the effective contractile elements of the uterus leave the spinal cord via sympathetic fibers at various levels higher than the tenth thoracic segment. Accordingly, it is possible to avoid inhibition of these impulses and diminution of uterine contractions by regulating the height of the effect through limitation of the volume of the injected agent.

The principal contraindications to continuous caudal analgesia include gross deformities or disease of the spine, sacrum, and central nervous system, fat pads obliterating the sacral hiatus, local infection at or near the site of needle insertion—including pilonidal cysts, psychic and emotional disturbances, a history of sensitivity to the drug. The procedure is withheld in the presence of such obstetric complications as placenta previa, abruptio placentae, severe cephalopelvic disproportion, floating head in a primiparous patient, predetermined monstrous and dead babies.

Results

In the present series, complete success was attained in 203 cases (81.2 per cent). This implies that labor was painless during the time caudal analgesia was used, and delivery was accomplished without discomfort to the patient and without recourse to supplemental anesthetic agent.

Listed as partially successful are 29 cases (11.6 per cent). In this group successful caudal analgesia during labor was deliberately terminated in 14 patients (5.6 per cent). In seven of these cases labor did not progress satisfactorily due to causes other than caudal analgesia, and it was deemed advisable to give the patient a complete rest. The caudal technique was discontinued and sufficient sedation to create a complete rest from labor was administered. In four other patients the analgesia was begun before labor had become well established, and the needle was removed after a period of lack of progress in the presence of ineffective uterine contractions. Emotional disturbance amounting to hysteria was the reason for terminating the caudal analgesia in two cases, and in one patient the needle was removed under the mistaken impression that a subsequent injection of the anesthetic agent had been made directly into the sacral plexus. Caudal analgesia was not restarted in any of these patients, and delivery was carried out with the aid of gas anesthesia.

Fifteen patients (6 per cent) on whom caudal analgesia was attempted obtained incomplete relief from pain or analgesia that could not be

maintained as long as necessary. Five patients in this group never were completely relieved of all discomfort, and four others became refractory to subsequent injections after a period of successful analgesia. In four cases the needle became dislodged toward the end of labor, and in two others the needle became plugged. It was necessary to deliver this group of patients with supplementary gas or open-drop ether anesthesia.

Complete failure occurred in 18 of 250 attempts (7.2 per cent). Two of these failures were due to introduction of the needle into an abnormally low-lying dural sac, resulting in the withdrawal of spinal fluid. No attempt to continue was made in these cases for fear of producing massive spinal anesthesia. Five patients were found to have congenital abnormalities of the sacrum, unrecognized before attempted insertion of the needle and incompatible with use of the caudal technique.

The remaining eleven failures were attributed to improper insertion of the needle. The subcutaneous tissue overlying the sacrum was the common site of misplacement. In no instance was a needle passed into the rectum. Most of the patients in this group were so obese over the sacrum as to make adequate palpation of the caudal hiatus difficult or impossible—in general, poor candidates for the procedure. Attempts at insertion of the needle in five of these cases were made during the terminal stages of labor in the presence of perineal bulging or crowning of the fetal head, which in itself constitutes one of the relative contraindications to the caudal technique. Postpartum roentgen studies in this group may have uncovered more abnormal sacra, since the incidence of congenital abnormalities of this bone incompatible with the caudal analgesia technique is greater than 5 per cent in females.[2]

As might be expected with increase in experience, there were less failures and unsatisfactory results in the last half of the series than in the first half.

Possible serious complications of the technique include inadvertent massive spinal anesthesia, intravenous injection (or rapid absorption through traumatized vessels) with subsequent vasomotor collapse or convulsions, infection of soft tissues, bone, or in the peridural space, and broken needles. (The latter complication is rare when the newer malleable steel needle and care are used.)

Postanalgesic neurological sequelae have been publicized among the laity, but in actual fact only one case of definite nerve damage subsequent to the caudal technique has been mentioned in the literature. Gready[3] reported a personal communication from Hawkins describing in the latter's private practice a case of postpartum saddle anesthesia and disturbance of sensation and motor function in the right leg. Such a lesion may be due in part to damage of nerve roots beyond the reach of the caudal needle and cannot be assumed to be due to mechanical trauma. At the time of Gready's report spontaneous regression in signs and symptoms was taking place, and prognosis for ultimate recovery was believed good.

Increased incidence of urinary retention postpartum has not been noted in this series or in others where physiologic or isotonic solutions have been used as vehicles, and distention of the bladder during labor has been prevented by periodic catheterization. It is our technique to use an inlying catheter which is drained at least every hour that it is in place.

In this series there was no maternal mortality from any cause and no morbidity requiring additional hospitalization that could in any way be attributed to the caudal analgesia technique. No spinal anesthesia was produced and no needles were broken.

Infection was limited to one case of superficial cellulitis that responded rapidly to cruciate incision and drainage, and to a case of gluteal bursitis in an obese patient who received a subcutaneous injection of the drug. The bursitis responded well to local heat.

One patient demonstrated generalized clonic convulsive movements lasting a few seconds, along with syncope, nausea, and vomiting. This was attributed to rapid absorption of the metycaine through an area of traumatized blood vessels. The patient recovered within a few minutes without untoward effects, and the delivery of a normal baby proceeded uneventfully under unsupplemented caudal analgesia. Five other patients demonstrated less severe toxic reactions, consisting of vertigo, tinnitus, and momentary syncope. Induction of analgesia is preceded routinely by administration of 0.1 to 0.2 Gm. sodium pentobarbital (nembutal), which increases the patient's tolerance to the anesthetic agent and serves to mitigate possible toxic reactions.

Blood pressure drop of significant magnitude—due to vasodilatation in viscera and lower extremities from lumbar sympathetic block—is a common occurrence and must be watched for by frequent manometer checks after each injection. Prompt administration of vasopressor agents or autotransfusion by elevation of the legs generally corrects the hypotensive condition.

One hundred and twenty-seven cases (54.7 per cent) of the 232 who actually received caudal analgesia exhibited a systolic blood pressure fall of greater than 20 mm. Hg, but all patients responded quickly to the treatment mentioned above, and no embarrassment of fetal circulation or untoward reaction in the mother was recorded.

Nine intrapartum and postpartum fetal deaths were recorded among the 250 deliveries in this series, giving a gross uncorrected fetal mortality rate of 3.6 per cent. When corrected for unavoidable deaths the fetal mortality rate is seen to be 2 per cent. None of the fetal deaths could in any way be attributed to the use of caudal analgesia.

TABLE I. SUMMARY OF FETAL DEATHS

DESCRIPTION OF FETUS	NUMBER OF CASES
(a) Previable Fetus	2
(Weight less than University of Michigan minimum standard of 1,000 Gm.)	
(1) 345 Gm.	
(2) 435 Gm.	
(b) Term fetus with abnormality incompatible with life confirmed by autopsy findings	2
(1) Congenital absence of diaphragm	
(2) Von Gierke's disease	
(c) Premature fetus	3
(Weight less than 2,500 Gm.)	
(1) 1,005 Gm.	
(2) 1,710 Gm.	
(3) 1,860 Gm.	
(d) Term or near-term fetus dying in the immediate postpartum period from overwhelming infection	2
(1) Bilateral confluent pneumonia	
(2) Multiple abscesses	

It has been noted by others and supported by our observations that one of the most striking, and certainly most significant, phenomena occurring in labor and delivery under continuous caudal analgesia is the rapidity with which the infant breathes and cries lustily after the head is born. The vital mechanisms of the fetus are not obtunded by narcotics or general anesthetic agents that might otherwise be used. Trauma to the fetal head likewise is minimized in the presence of relaxed and softened musculofascial pelvic structures and with the absence of violent expulsive efforts on the part of the mother. These factors make continuous caudal analgesia highly desirable in premature labor, where the underdeveloped fetal structures are particularly delicate.

Because the parturient loses the urge to bear down, it was feared early in the development of caudal analgesia that operative interference

for delivery would be increased to such an extent as to constitute a definite hazard to mother and fetus. With proper management of labor and delivery, major operative interference need not be increased. In 200 cephalic presentations in this series where actual delivery took place under unsupplemented caudal analgesia, forceps were used in 154, or 77 per cent, of the cases. This compares with 20.7 per cent forceps deliveries in this clinic during the whole year of 1942—before any caudal analgesia was used.

While operative interference in our series rose from 20.7 per cent to 77 per cent, this increase loses much of its significance when it is noted that no "high" or "midforceps" were necessary in the caudal series. Sixty-three of the 154 forceps deliveries in this group were classified as "low forceps" and the other 91 were of the "outlet" variety, consisting of "lifting" the presenting head through the introitus after perineal bulging or crowning of the fetal scalp had occurred.

Failure of complete and spontaneous rotation of the head due to loss of tone and resistance in the musculofascial sling of the birth canal has been mentioned as a drawback of caudal analgesia and a potential source of traumatic operative interference. In the 154 cephalic cases terminated by forceps delivery, only 19 failed to show spontaneous rotation of the presenting part (occiput in all cases) into one of the anterior quadrants of the pelvic outlet. This amounts to 9.5 per cent of all cephalic cases actually delivered under caudal analgesia alone. The incidence of failure of spontaneous rotation in cephalic presentations in this clinic was 3.6 per cent in 1942.

In six of these 19 cases of failure of rotation beyond the transverse position, manual rotation preceded forceps delivery, and in 12 others forceps rotation was carried out. One infant was delivered as a persistent occiput posterior. It should be emphasized that all of these operative procedures were carried out with the head low in the pelvis and were simplified and made less traumatic than under inhalation anesthesia because of the relaxation of pelvic soft tissue structures produced by the caudal technique.

Our observations on length of labor under continuous caudal analgesia support the findings of Hingson and Edwards.[4] The average duration of labor as a whole, and of the first stage (stage of cervical dilatation) in particular, is shorter than with other forms of analgesia. Only when the presenting part is allowed to rest neglected on the perineal floor need the second stage of labor be significantly increased in duration. The average multipara, alert and cooperative under this form of analgesia, can generally expel the fetal head over the perineum by the voluntary fixation of the diaphragm and contraction of abdominal muscles, when informed of the occurrence of a (painless) uterine contraction by the attending accoucheur. The uninitiated primiparous individual does not coordinate so well her efforts, but, with little or no effort on her part, the presenting part generally is brought to the perineum and can be "lifted" gently through the introitus by "outlet" forceps.

The third stage of labor likewise is shortened under continuous caudal analgesia. The absence of inhibition of the contractile elements of the uterus decreases the period of postdelivery uterine relaxation or atony, and third-stage blood loss is diminished in most cases. Average estimated

blood loss in those cases in this series delivered under unsupplemented caudal analgesia was less than 150 c.c. In 500 cases Lull[5] found an average blood loss of 111 c.c. These figures compare favorably with average blood loss during labor (about 300 c.c., DeLee) with other forms of analgesia and anesthesia. Much of the blood loss under caudal analgesia comes from dilated vessels cut during episiotomy, and can be controlled by hemostatic clamping and ligation of the larger vessels and by sponge pressure on the cut surfaces.

Since the effectiveness of continuous caudal analgesia tends to decrease as its duration in any given patient is prolonged (refractory response to subsequent injections tends to increase progressively after 8 to 10 hours), it is our policy to delay the induction of analgesia until labor is well established and the patient is experiencing pain and not mere discomfort. In primiparous patients the introduction of the needle is not made until the cervix is well effaced and dilated at least 3 to 4 cm., and the head is well engaged in the pelvis. In multiparas the analgesia is induced as soon as significant progress is noted. This obviates the need of haste in the late stages.

Duration of successful analgesia in this series ranged from twenty minutes to twenty-two hours. The average length of time was two hours and thirty-six minutes in multiparas and five hours and forty minutes in primiparas.

Approximately 0.36 Gm. of metycaine is used every hour, calculated on the basis of a 30 c.c. initial injection of the 1.5 per cent solution and the requirement in the average case of a subsequent dose of 20 c.c. every fifty minutes.

We have mentioned the value of experience in attaining good results with continuous caudal analgesia. Careful attention to the patient is an equally important prerequisite to success and complete safety. All of the cases in this series have been managed by three properly trained members of the instructor and resident staff. The responsibility of the anesthetist-obstetrician in each case does not end with the insertion of the needle, but, rather, the patient is followed closely through labor and delivery. Subsequent injections of the anesthetic agent are given by the attending staff physician in each case and the effects evaluated by him. Any aberration from the usually expected results are noted and corrective procedures carried out as necessary. Turning the patient from side to side during labor, transporting her to the delivery room and placing her properly upon her back are carried out under the direct supervision of the physician. Blood pressure readings are taken at ten- to fifteen-minute intervals after each injection and after the patient has been placed upon her back for delivery. Therapeutic measures for fall in blood pressure are instituted promptly.

In any consideration of the advantages and difficulties of continuous caudal analgesia, certain more or less intangible factors not suitable for statistical evaluation should be mentioned. Older obstetricians familiar with the discomfort associated with labor during precaudal days cannot help but be impressed, and relieved, by the well-being of patients in labor under continuous caudal analgesia. The parturient remains at ease mentally as well as physically. Fear and anxiety are absent. Emotional tension is minimal, and the restlessness and irrational

cries so often associated with use of amnesic and analgesic drugs do not cloud the picture of labor for the patient and her attendants. The fully conscious patient is able to take nourishment and adequate amounts of fluids during the course of labor. Reflex vomiting is infrequent. As the end of labor approaches, the patient may be moved into the delivery room without haste, and preparation of the patient can be quietly and adequately carried out. Delivery is performed with deliberation and care. Following delivery the mother may be able to eat and drink immediately, and postpartum convalescence appears to be hastened because the patient under continuous caudal analgesia suffers a minimum of mental and physical exhaustion.

Summary

In summary, certain characteristics of continuous caudal analgesia in obstetrics reported by others are further supported by our experience with 250 consecutive cases:

1. Complete relief of pain during labor and delivery may be obtained, without impairment of consciousness or abolishment of voluntary motion, and without interference of uterine contractions.

2. The respiratory and other vital mechanisms of the child are not depressed.

3. Labor is shortened in most cases.

4. Blood loss during labor is decreased, and postpartum hemorrhage is minimized.

5. The incidence of operative delivery is definitely increased, but consists chiefly of outlet forceps. There was no increase in any of the major or more serious obstetric operative procedures in our series.

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CESAREAN SECTION UNDER FRACTIONAL SPINAL ANESTHESIA

WILLIAM LEVINE, M.D., F.A.C.S., BROOKLYN, N. Y.
(From the Department of Obstetrics and Gynecology at the Beth-El Hospital)

THE use of single dose spinal anesthesia in cesarean section has long been advocated by Cosgrove.[1] Although it is ideal for the operator because of the marked abdominal relaxation, diminution of blood loss and noninterference with initiation of respiration of the newborn infant, maternal deaths and near-deaths have been reported. Waters[2] reported one death in 3,000 cases and in addition refers to several close calls and near-deaths from the use of single dose spinal anesthesia. Plas and Ricci[3] report three deaths from bulbar syncope despite careful selection of patients and extreme caution in its administration.

Beck,[4] Gordon and Rosenthal,[5] DeLee,[6] Greenhill,[7] and many others agree that proper selection of the anesthesia reflects a good result, but condemn spinal anesthesia because of its particular danger in pregnant women. Greenhill stresses sudden death as a great danger in spinal anesthesia and attributes it to respiratory paralysis. Although single dose spinal anesthesia proved satisfactory in our experience we abandoned its use because of the above and many other adverse reports.

The return to the use of general anesthesia has been very disappointing because of the many complications encountered, as will be shown later. Local infiltration was found to be time-consuming and did not always produce proper anesthesia. Some advocate supplementing it with general anesthesia, particularly at the time the fetus is removed and when the placenta is extracted. In 1942, Lemmon and Paschal[8] reported 1,000 surgical cases including 62 cesarean sections, operated upon under continuous spinal anesthesia. A more recent report by Lemmon and Hager[9] supplements the original report and summarizes their results in 2,000 surgical cases which include 140 cesarean operations.

This method has the advantage of administering a small amount of anesthetic solution and adding more if and when needed. They contend that all forms of anesthesia are administered fractionally as the patient requires it. For instance, inhalation anesthesia is continued in concentrations and for as long a time as the surgeon needs it to complete the operation. Similarly, in local anesthesia, more anesthetic fluid is added when the patient complains of pain. Even in intravenous anesthesia the amount given is as required, and not necessarily the entire dose empirically prescribed. An initial small dose of the drug with the spinal fluid can be withdrawn should unforeseen toxic symptoms appear, because the flexible needle remains in situ throughout the operation. The fractional administration of the drug has particularly appealed to us. The continuous feature which is of benefit in prolonged operations is not necessarily applicable in cesarean operations. Table I reveals the types of anesthesia in our last 286 cesarean operations. We wish to report mainly our results in the 144 operations done under fractional spinal anesthesia, and compare them with the results in the 103 operations performed under general anesthesia.

TABLE I. TYPES OF ANESTHESIA

Fractional spinal	144
General	103
Local infiltration	19
Caudal	14
Local and general	4
Unrecorded	2
Total	286

We have used 8 c.c. of spinal fluid to dissolve 200 mg. of procaine crystals. Each cubic centimeter of this solution therefore contains 25 mg. of procaine. The spinal canal is entered between the third and fourth or fourth and fifth lumbar interspace, with the patient lying in left lateral position. The connecting tube is then attached to the flexible spinal needle. The patient is then placed in the dorsal recumbent position and 2 c.c. (50 mg.) are injected slowly through a syringe connected at the opposite end of the tubing. This produces a closed sterile circuit and subsequent injections of 1 c.c. are given as needed, usually within thirty minutes after the first injection, and still further injections of 1 c.c. are given at fifteen-minute intervals.

The Trendelenburg posture is not needed. The natural curvature of the spine will cause the procaine solution to rise cephalad, sufficiently high to produce adequate anesthesia for operation. The level usually reached is about that covered by the eighth thoracic nerve.

Preoperative administration of ephedrine sulfate is rarely necessary, for the fall in blood pressure is minimal with a 50 mg. dose. If the blood pressure at the start of the operation is below 120 systolic, ephedrine sulfate, ¾ grain, is administered. Slight nausea is sometimes encountered, and this is combated by inhalation of a pungent medicament such as aromatic spirits of ammonia. Oxygen inhalation sometimes controls this nausea.

Venoclysis is rarely needed unless as a preliminary to a planned blood transfusion. Morphine sulfate, ¼ grain, is administered as soon as the baby is extracted and oxytocic drugs are administered soon after the placenta is removed. The patient remains relaxed, comfortable, and composed throughout the operation. When the patient complains of pain the additional dose of 25 mg. of procaine is conveniently added.

Fifty milligrams of the drug administered initially is generally sufficient for all the intra-abdominal work. The additional 25 mg. is given for closure, and only when necessary. Table II shows that in 8 instances the operation was completed with only 50 mg. of procaine. In 72 instances the operations were started with 50 mg. of the drug and were completed by adding 25 mg. more after thirty minutes. Forty-one cases required up to 100 mg. of the drug in divided doses. There were also 23 patients who required over 100 mg. of the drug for the completion of the operation. This does not imply that many operations consumed over one hour of operating time. In instances where more than 100 mg. of procaine were used, the patients had a special insensitivity to the drug, or they were obese and large, thus requiring more drug to produce suitable anesthesia.

TABLE II. AMOUNT OF DRUG USED

MG.	MG.	MG.	MG.
50	50-75	50-100	Over 100
8	72	41	23

Table III reveals that the operating time in 14 patients was over one hour, and in only 32 instances the operations lasted thirty minutes or less. There were 72 operations which lasted between thirty and forty-five minutes, and 26 operations lasted forty-five to sixty minutes. The average operating time was 44.5 minutes.

TABLE III. TIME OF OPERATION

30 MIN. OR LESS	30-45 MIN.	45-60 MIN.	MORE THAN 60 MIN.	AVERAGE TIME
32	72	26	14	44.5

There is a remarkable diminution in blood loss during the operation. The uterus after extraction of the baby and placenta is firm, hard, and pale instead of the usual soft, beefy red color of the gravid uterus. It remains so throughout the operation and the field is free from blood. Only 8 transfusions were needed in the series of 144 cesarean operations under fractional spinal anesthesia, and 5 of these were for replacement due to loss in antepartum bleeding. In the 103 patients operated upon under general anesthesia 18 transfusions were given. Eight of these were given for antepartum hemorrhage, and the remaining 10 for bleeding incident to loss of blood during the operation, as illustrated in Table IV.

TABLE IV. TRANSFUSIONS

	FRACTIONAL SPINAL	GENERAL
Antepartum bleeding	5	8
For blood loss at operation	3	10
Total	8	18

The postoperative course is unusually smooth. Food is tolerated much sooner after the operation. Distention is at a minimum and the postoperative recovery is unusually rapid. The average postoperative hospital stay was 11 days. The shortest stay in the hospital was 9 days, and the longest stay was 26 days. In the group of 103 patients that received general anesthesia, the postoperative stay was much longer. Here the average stay was 14 days, the longest stay was 58 days, and the shortest stay was 11 days.

TABLE V. RESULTS IN INHALATION ANESTHESIA SERIES

No Complications		85
Complications (Several had more than one complication)		15
Endometritis	5	
Wound infection	4	
Bronchopneumonia	3	
Postoperative uterine bleeding	2	
Acute gastric dilatation	1	
Paralytic ileus	1	
Thrombophlebitis and pulmonary infarction	1	
Pyelitis	1	
Trigonitis	1	
Abdominovesical fistula	1	
Deaths		3
Cardiovascular collapse	1	
Peritonitis	2	

The results from general anesthesia are listed in Table V. There were 85 patients who had no complications, and 15 patients had one or more of the complications listed. Some of these complications cannot be attributed to the form of anesthesia used. However, in the instances of bronchopneumonia, postoperative uterine bleeding, endometritis, acute gastric dilatation, and a few others, the anesthetic is directly the cause or has prepared a basis for the complication. The three maternal deaths in this group were not directly related to the anesthetic. They were not anesthetic deaths. One patient died of cardiovascular collapse. She was suffering from rheumatic heart disease and had decompensated on two occasions during her pregnancy. She was in the hospital for observation and treatment prior to operation, and was operated upon under novocain infiltration anesthesia supplemented by nitrous oxide and oxygen. She died twenty-four hours later of cardiovascular collapse. The other two patients died on the seventh and eighth postoperative days, of peritonitis.

Table VI indicates the results under fractional spinal anesthesia. There were 138 patients with no complications. Two had abdominovesical fistulas following the Waters' extraperitoneal operation; one had mastitis; one had an abdominal wound infection; and there was only one instance with marked abdominal distention which abated on the seventh postoperative day. In this group of 144 cases there was only one death, which cannot be attributed to the anesthesia. This patient died on the tenth postoperative day of uremia following the administration of Rh incompatible blood.

TABLE VI. RESULTS IN FRACTIONAL SPINAL SERIES

NO COMPLICATIONS	COMPLICATIONS				DEATHS
	Abdominovesical Fistulas	Mastitis	Marked Intestinal Distention	Wound Infection	Uremia due to Rh incompatibility
138	2	1	1	1	1

Summary

1. Fractional spinal anesthesia has been satisfactorily used in 144 cesarean operations.

2. An initial dose of 50 mg. of the drug did not produce toxic manifestations or cause severe drop in blood pressure, and was sufficient for all the major intraperitoneal work. Additional anesthetic was conveniently added as needed.

3. There was a minimal amount of bleeding and greater facility during the operation. The uterus remains well contracted during the operation and throughout the puerperium. There were no instances of early or late postoperative bleeding.

4. There were fewer transfusions given in this series in contrast with the number given in the series which were operated upon under general anesthesia.

5. The postoperative course was smoother, complications fewer, and hospital stay shorter.

6. There was one maternal death in this series, not in any way related to the anesthetic.

Appreciation is expressed to Dr. Jacob Herzlich for planning the technique and administering all fractional spinal anesthesias in this study.

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960 STERLING PLACE.

THE CIRCULATION OF AMNIOTIC FLUID

WILLIAM F. MENGERT, M.D., AND J. W. BOURLAND, M.D.
DALLAS, TEXAS

(From the Department of Obstetrics and Gynecology of the Southwestern Medical College and the Dallas Medical and Surgical Clinic)

FOUR theories are current concerning the origin of amniotic fluid. According to these, it is: (1) derived from fetal urine, (2) a transudate from maternal blood, (3) secreted through the amniotic epithelium, (4) of mixed origin. Williams[7] believes that, "from the evidence at present available, it would appear that under normal conditions the amniotic fluid is derived primarily from the maternal serum, which may be modified during its passage through the amniotic epithelium; but that under abnormal conditions other sources, more particularly the fetal urine, will have to be taken under consideration." This is the most generally accepted theory, except that many do not subscribe to the idea that fetal urine contributes significantly.

If amniotic fluid is derived from the maternal serum, it follows that there is probably continuous production, and unless hydramnios develops, continuous disposal. Taussig[5] believes, "that normally there is an outflow as well as an inflow" of amniotic fluid. Polano[4] and DeSnoo[1] concur, and these three authors believe that amniotic fluid normally is ingested by the fetus and eliminated by way of the fetal and maternal blood streams. DeSnoo believes that the principal, and practically the only, channel of elimination is by way of the fetal intestinal tract. Demonstration of lanugo hairs and epidermal cells in the fetal stomach and intestines at postmortem examination, and of epithelial cells in meconium of the living newborn infant,[3] offers ample evidence for the ingestion of amniotic fluid during pregnancy. Other evidence concerning disposal mechanisms has been obtained by following the fate of dyes experimentally introduced into the amniotic cavity.

Since there seems to be little question concerning the continuous disposal of amniotic fluid, there must be some mechanism to regulate the amount produced in normal pregnancy. DeSnoo believes that the quantity swallowed by the fetus affects production. In other words, if intra-amniotic fluid pressure is low, there will be increased transudation from the maternal serum; if high, diminished transudation.

Normally, these regulatory mechanisms are adequate for the relatively minor variations in quantity of fluid swallowed by the fetus. On the other hand, in the presence of serious obstruction of the absorptive process, hydramnios could result. Massive interference with outflow might be expected to diminish production, but probably not to eliminate it altogether.

Obviously, congenital atresia of the fetal gastrointestinal tract would represent a massive blockade to the outflow of amniotic fluid. As a corollary, it might be postulated that such obstruction must be situated relatively high in the gut, since blockage of the large bowel, for example, would interfere with neither ingestion nor absorption.

It was, therefore, with considerable interest that each of the authors observed the development of hydramnios in a pregnant woman whose baby was born with a duodenal atresia. The following two case reports are presented because we believe that the gestational effects of the natural experiment resulting from the anomaly lend considerable support to the theory of continuous production and absorption of amniotic fluid during normal pregnancy.

CASE 1.—Mrs. G. N., Hospital No. G510,* a gravida iii, aged 36 years, with two living children, was first seen at the University of Iowa Hospitals, Sept. 16, 1937, at about the twentieth week of her fourth pregnancy, at which time nothing abnormal was noted. Eight weeks later it was noted that the uterus was unduly large, with the fundus higher than expectancy for the calculated duration of pregnancy. By the thirty-third week of gestation there was definite hydramnios. A fetus corresponding in size to the duration of pregnancy could be palpated, although the uterus was as large as, or larger than, a pregnancy at term. A roentgenogram of the abdomen revealed no evidence of fetal skeletal deformity.

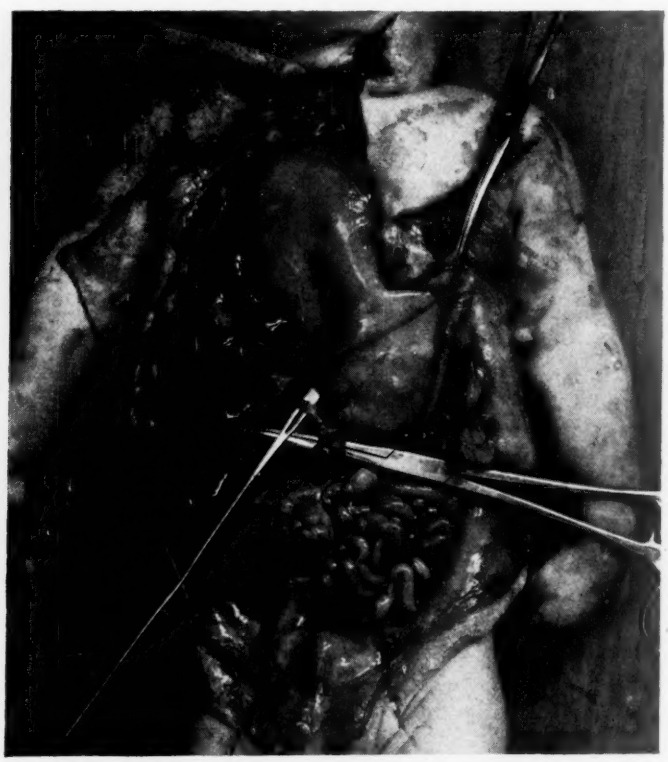

Fig. 1.—The liver has been displaced to the right. The stomach and duodenum have been lifted up and to the left so that the posterior surfaces are visible. The "shaft" of what looks like a dumbbell is the distended pylorus. The transverse line across the distended portion of the duodenum is an artifact produced by traction on the superior hemostat.

The atretic portion of the gut lies immediately superior to the inferior hemostat, between it and the distended duodenum. The probe lies under the common duct.

Labor began prematurely at the thirty-sixth week, probably because of excessive uterine distention, and resulted in the spontaneous birth of an apparently normal male child weighing 2,750 grams. There were approximately 2,000 c.c. of amniotic fluid. The maternal puerperal course was uneventful.

*Permission to use this case report was kindly granted by Dr. E. D. Plass, Iowa City, Iowa.

The infant cried spontaneously and presented no evidence of abnormality. Fourteen hours after birth he regurgitated a small amount of a feeding, but had taken those before, and took some after, without difficulty. Regurgitation after feedings became the rule thirty-one hours after birth and increased both in frequency and in force until almost all of each feeding was returned with a projectile type of vomiting. Feeding by gavage was attended with a similar result. Small stools of meconium were passed. The infant's condition rapidly became worse, with cyanosis, apnea, and weak heartbeat, and death occurred 77½ hours after birth. An atresia of the duodenum, 5 cm. distal to the pylorus, was discovered at postmortem examination. The block was complete and permitted passage of neither a probe nor water. In addition, there was pulmonary congestion and edema which may have resulted from aspiration of regurgitated food. The report of the pathologist follows:

"The stomach was considerably distended, and the duodenum was widely distended to a point 5 cm. distal to the pylorus. Gas, and white semifluid material filled the stomach and the distended duodenum. The pylorus was distended and patent with walls of normal thickness. The duodenal lumen was completely closed just proximal to the entrance of the common duct as demonstrated by inability to pass a probe or fluid. Below the point of atresia the gut was quite small and contained only a very small amount of meconium."

"The common duct entered the duodenum 5 mm. distal to the atresia, and the duct of Wirsung joined the common duct 4 mm. from the ampulla of Vater. The remainder of the gastrointestinal tract, including the anus, was freely patent. The gall bladder contained a normal amount of bile. The rest of the body was essentially normal."

Anatomic Diagnosis.—Congenital atresia of the duodenum 5 cm. distal to the pylorus; pulmonary congestion and edema (Fig. 1).

CASE 2.—MRS. W. R. E.* was first seen Dec. 6, 1937, in the sixth week of pregnancy, at which time she weighed 115½ pounds. The pregnancy proceeded normally with questionable distention of the uterus until the twenty-seventh week, when it was noted that the uterus was markedly distended with fluid. By the thirty-first week there was definite hydramnios and the fetal heart tones could not be heard. During the thirty-sixth week the patient weighed 164 pounds (a gain of 48½ pounds) and was complaining of dyspnea. The membranes were ruptured artificially and the patient was delivered spontaneously of an apparently normal 2,841-gram female child after an escape of 4,600 c.c. of fluid. The maternal postpartum course was uneventful.

Regurgitation of food with strangling and cyanosis began on the second day of life, and the vomitus soon became bile stained. There was one small stool of meconium. A diagnosis of congenital obstruction of the duodenum was made and duodenojejunostomy performed by Dr. J. W. Duckett on the fourth postnatal day.

Operative Findings.—"The stomach and proximal portions of the duodenum were found to be greatly dilated and thick-walled. There was an abnormally high attachment of the mesentery of the ascending colon and cecum; and, apparently because of this attachment, there was a fold of peritoneum overlying the duodenum at its most posterior location producing some occlusion of the lumen. It is probable that the obstruction of the lumen was due mainly to an intrinsic defect such as persistent diaphragm. The jejunum and large intestine were normal in appearance wherever seen." A duodenojejunostomy, anastomosing the second portion of the duodenum with the proximal end of the jejunum, was performed. "When the duodenum was opened, a catheter was passed upward into the stomach, meeting no obstruction;

*Permission to use this case report was kindly granted by Dr. J. W. Duckett,[2] and the J. B. Lippincott Company, publishers of the *Annals of Surgery*.

and was then passed downward to the point of obstruction at the base of the mesocolon.'' (Fig. 2.)

Breast milk was fed during the postoperative course and was vomited only twice. Supportive treatment included the administration of CO_2 and O_2 and infusions of saline and dextrose. The child has been seen frequently since; her development has been entirely normal and she has enjoyed excellent health.

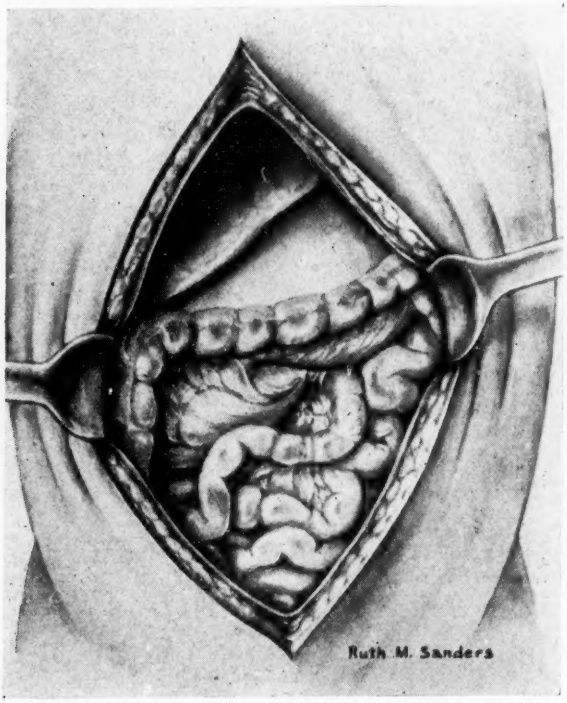

Fig. 2.—The atretic portion of the duodenum is seen just below the greater curvature of the stomach, the edge of which is visible below the transverse colon. The distended upper portion of the duodenum is seen beneath the angle formed by the ascending and the transverse colon. (Reproduced from the *Annals of Surgery*[2].)

Discussion

The case histories of these two children, with regard to the mothers' pregnancies, the symptoms during the first few days of life, and anatomic findings were strikingly similar. Each had an atresia of the duodenum. It seems reasonably safe to conclude that the maternal hydramnios resulted in each case from the inability of the fetus to ingest and absorb amniotic fluid. That fluid was swallowed is attested to by the remarkable distention of the stomach and proximal portion of the duodenum of each child. These two natural experiments give strong support to the theory that normally there is an outflow as well as an inflow of amniotic fluid.

On the other hand, the general belief that a large part of the fluid necessary for fetal development is obtained through ingestion of amniotic fluid is not sustained, since each of these children was normally developed at birth at the thirty-sixth week of gestation and weighed 2,750 and 2,841 grams, respectively. Since these weights are normal for infants born about the thirty-sixth week, it would seem that failure to absorb usual quantities of amniotic fluid did not interfere with general development.

From the clinical standpoint, it is likely that hydramnios developing during the second half of pregnancy, coupled with early and persistent postnatal regurgitation in an otherwise normal-appearing infant, should offer strong evidence of an intestinal atresia located near the stomach. Such infants should be operated upon without delay. On the other hand, hydramnios may be absent in atresias of the jejunum and below, since in such cases sufficient portions of gut remain available for absorption. Therefore, although this syndrome seems to be definitive for high duodenal atresia, absence of hydramnios does not exclude the possibility of intestinal block at a lower level. At the time of Webb and Wangensteen's[6] report in 1931 on "Congenital Intestinal Atresia," there had been only nine reports of successful surgical attack upon this anomaly. Since then there has been a gratifying increase in the number of reports of infant salvage. Atresias of the intestine are fortunately rare and it is estimated[6] that they occur with a frequency of about 1 in 20,000.

Summary and Conclusions

Present concepts of the origin and circulation of amniotic fluid are discussed. The anatomic findings in two infants with duodenal atresia, whose mothers developed hydramnios during the second semester, are presented to support the theory that there is a constant absorption as well as production of amniotic fluid during normal pregnancy.

Failure to absorb usual quantities of amniotic fluid did not influence the gestational development of these two infants.

The association of hydramnios with subsequent birth of a normal-appearing infant who speedily develops persistent and forceful vomiting appears to be a syndrome characteristic of atresia of the upper portion of the duodenum.

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VITAMIN E IN MENOPAUSE

Preliminary Report of Experimental and Clinical Study

CHRIST J. CHRISTY, M.D., BUFFALO, N. Y.

(From the State Institute for the Study of Malignant Diseases)

THE advent of modern endocrinology and biochemistry made possible a variety of estrogenic substances such as hormones or synthetic agents in the treatment of menopausal syndrome. The purpose of this paper is to report the writer's observation and clinical experience in the use of vitamin E as a therapeutic agent in a group of cases with severe symptoms of menopause. A large number of instances in the menopausal group of cases are seen at this clinic because of abnormal uterine bleeding induced by improper or prolonged dosages of estrogens. These patients are referred by their physicians with a suspicion of carcinoma of the uterus and of course are subjected to diagnostic curettage to rule out malignancy.

Consideration of uses and limitations of estrogenic therapy as outlined in a recent article by Novak[1] can be heartily endorsed, and such is the policy of the author in dealing with such cases. Estrogen is valuable at times in facilitating the hormonal adjustments of a large number of patients; however, like so many other valuable therapeutic agents, their prolonged and indiscriminate use is unnecessary and actually harmful. In regard to the so-called carcinogenic effect of estrogen, Novak[1] further states there has been considerable discussion as to whether or not excessive therapy can actually incite the development of cancer. Without reviewing this very broad problem, suffice it to say that the consensus is that no such hazard pertains to the clinical employment of estrogens in any customary therapeutic dosage. He further adds that since our knowledge of the possible carcinogenic role of the estrogens is still very incomplete, it is a wise policy to avoid unnecessarily large doses, and to eliminate such treatment altogether or hold it to a minimum for persons who harbor any so-called precancerous lesions, or for those who have a clear-cut family history of cancer.

The question whether overstimulation of the aging endometrium by estrogens may enhance the evidence of carcinoma in human beings, as they have characterized the production of carcinoma in experimental animals, seems to be still unsettled, if one reads the vast amount of research on the subject.

The author's hope that vitamin E may be an effective remedy in treatment of the distressing symptoms of menopause was instigated by reading a report of a clinical and laboratory study on amenorrhea by Whitacre and Barrera.[2] This report deals with treatment of a large number of women internees in the Santo Tomas Internment Camp at Manila, Philippines, who were suffering from amenorrhea, probably due to severe psychic shock, worry, or fear. Due to a small supply of estrogenic substance available, ten patients of this group were given vitamin E in the form of wheat germ oil: a dose of 20 drops orally, three times daily, for a period of ten days preceding the expected menstrual flow. Eight of the ten patients had a menstrual period or a uterine bleeding. The exact role of vitamin E in the human organism is unknown, but Mattill,[3] in reviewing the work on the subject, states that any definite connection of vitamin E with sex hormones and thyroid gland or any relationship to malignancy is not supported by the experimental evidence presented. He further states,

however, that the finding of hypoplastic thyroids in female E-deficient rats[4] with return to normal appearance on administering vitamin E, suggests that thyrotropic as well as gonadotropic activity of the pituitary may be altered in the absence of vitamin E.

The author, impressed first with the favorable response obtained from vitamin E therapy in "War Amenorrhea," and second by our incomplete knowledge about the chemistry and physiology of this substance, began to investigate the effect or potentialities of vitamin E in the menopause, as therapy with estrogens in a large number of his cases, due to the cancerous nature of the lesion, was wholly contraindicated.

In this study of six months' time, vitamin E in 10 mg. tablet form as ephynal acetate (Roche), a synthetic preparation, was given by mouth to 25 patients ranging in age from 22 to 55 years. Of this group 12 had carcinoma of the cervix, one had adenocarcinoma of the fundus, one had malignant leiomyoma and sarcoma of the uterus, six had fibroids, one had carcinoma of the ovary, one had hemangio-endothelioma of the parametrium, one had postmenopausal bleeding after estrogenic therapy, one had dysfunctional uterine bleeding due to endocrine disorder, and one had endometriosis. No patient was treated who did not complain of severe symptoms of vasomotor instability.

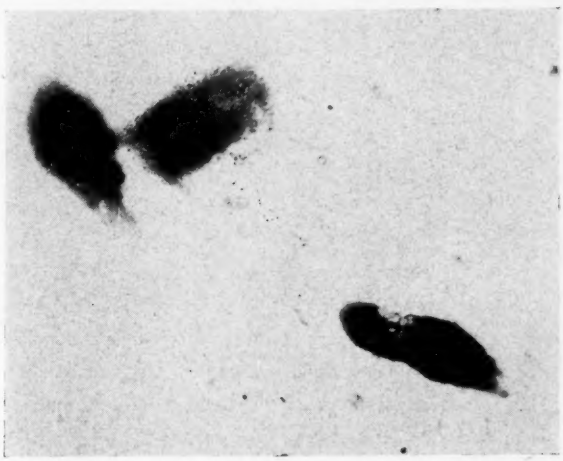

Fig. 1.—Case No. 49898. Patient, aged 37 years. Artificial menopause, induced by x-ray and radium. Very marked relief of menopausal symptoms after a total dose of 550 mg. of ephynal acetate Roche). Vaginal smear (fuchsin stain), showing only a few degenerated epithelial cells; no vitamin E response.

The amount of the drug taken varied from 10 to 30 mg. a day, depending upon the degree of severity of symptoms, over periods of from one to six weeks. All patients in this study were handled in a uniform manner, and the clinical effectiveness of the drug was recorded by one observer. Of the 25 patients, one suffered from symptoms of natural menopause, five from surgical and irradiation menopause, eleven from x-ray and radium menopause, eight from radium menopause.

First reports of experimental use of this drug were astonishing. The entire group of cases responded to the treatment and showed either complete relief or very marked improvement with less frequency and less severity of the hot flashes and drenching perspiration, and a definite change for the better in their mood and outlook.

Of these 25 patients, seven reported complete relief of symptoms on dosages of 10 to 20 mg. daily over periods of from one to three weeks. Sixteen patients

reported very marked relief on 10 to 20 mg daily over periods of from two to six weeks. A great reduction in the number of hot flashes per day was evident promptly upon taking the prescribed medication, and the patient's general condition greatly improved. These remarkable results obtained in these sixteen patients suffering with severe symptoms of menopause are sufficiently striking to justify calling attention to two of them. One patient (Case No. 46544) states: "I have noticed a diminishing of the hot flashes both in frequency and intensity." Another patient (Case No. 49671) writes: "Where six to eight flashes per day were very common before, I experience one per day after taking the medication."

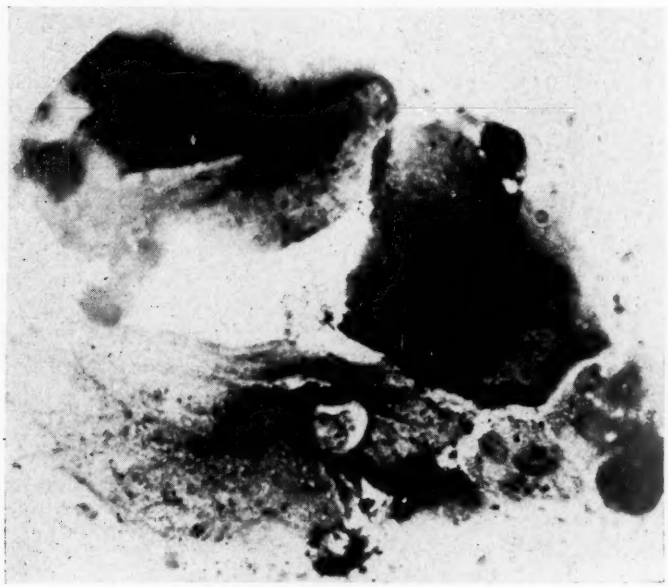

Fig. 2.—Case No. 49987. Patient, aged 40 years. Artificial menopause, induced by x-ray and radium. Family physician gave patient several "shots" of estrogenic preparation twice a week. Vaginal smear (fuchsin stain) showing cornified epithelial cells, occasional leucocytes; full estrus response. Suggested discontinuance of the "shots" and synthetic vitamin E prescribed instead. The replacement therapy with vitamin E was as effective as with the "shot" treatment.

It is the author's opinion that all of the latter group might have obtained complete relief on higher dosages, and subsequent indications point towards such a response, but at present they cannot, of course, be included with the complete relief group. In only two cases was treatment interrupted: Case No. 46661, with moderate relief, because of family and marital upset, and Case No. 43065, with slight or no relief, stopped treatment after a few days on 10 mg. daily. These patients were both advised to continue the treatment with comparatively higher dosage, 30 mg. per day. The author is of the opinion that both of these patients, with higher level dosage and under normal home life, will respond to treatment as did the rest of the group.

In discussing the results of therapy in menopause with synthetic vitamin E, it must be pointed out that the measure of clinical response was based largely on subjective findings. In a few instances, vaginal smears or endometrial biopsies, taken during the course of this study, revealed that vitamin E induced no change in the vaginal mucosa (Fig. 1) and endometrium. This was in contrast to the effect seen after estrogenic therapy on the vaginal epithelium (Fig. 2) and in the endometrium (Fig. 3).

Undesirable side reactions such as headache, nausea, vomiting, dizziness, soreness of the breasts, pelvic pain, and vaginal bleeding were not encountered in any of these patients.

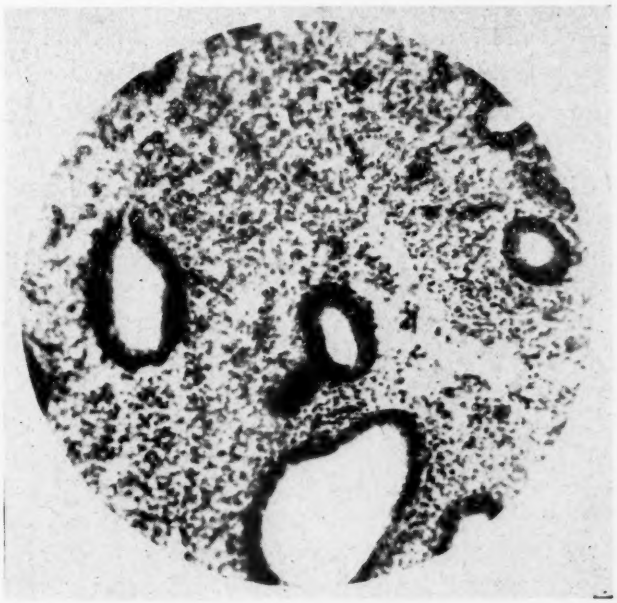

Fig. 3.—Case No. 51183. Patient, aged 50 years. Natural menopause three or four years previously. Five years ago, because of premenopausal symptoms, treatment by hypodermic injections of estrogenic preparation was begun by family physician at regular intervals and kept up because of skipping menstrual periods, menorrhagia, and metrorrhagia. Within the last few months this method of treatment was replaced by one tablet of estrogenic substance taken orally every morning. A few days before admission patient had a profuse vaginal hemorrhage. Endometrial biopsy showing endometrial glands are hyperplastic. The endometrial stroma shows intercellular hemorrhage; full estrus response.

Conclusion

This is a preliminary report of the clinical use of vitamin E in the treatment of menopausal syndrome. Vitamin E plays a physiologic role in women presenting symptoms of menopause. The nature of this action is not understood. The author believes that vitamin E has demonstrated its effectiveness in menopausal therapy by experimental and clinical application. The relief of symptoms in patients after administration of vitamin E could not be distinguished from that obtained with the natural or synthetic estrogens. In some cases vitamin E seems more effective in relieving the symptoms of vasomotor instability than estrogens. The chief advantage of the new drug over estrogen is in the fact that vitamin E is free of any stimulative effect or change on the genital system or in the parenchyma of the breast. It plays no possible carcinogenic role as the estrogens may do, and, due to the latter factor, vitamin E can be used freely in menopausal patients suffering from neoplastic disease. It produces no untoward aftereffects and is well tolerated.

Ephynal Acetate (Roche) used in this clinical investigation was supplied by Hoffman, LaRoche, Inc., through the courtesy of Dr. R. J. Floody.

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SULFONAMIDE AND STILBESTROL THERAPY IN GONOCOCCAL VULVOVAGINITIS*

LUCILE R. HAC, PH.D., H. CLOSE HESSELTINE, M.D., FRED L. ADAIR, M.D., AND MYRTLE B. CRUDIM, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital, and the Chicago Municipal Social Hygiene Clinic)

FOR the past several years, we have been studying the problem of gonococcal infection in children.† Some of the preliminary results have been reported elsewhere.[1, 2] This is the final report of our investigations of sulfonamide‡ therapy in this infection.

The use of cultural methods for the diagnosis of gonococcal vaginitis and proof of its cure have led to a truer concept of the incidence of the infection and is gradually eliminating the all too prevalent opinion that all or most vaginitis in children is gonorrheal in origin. Very frequently children recovering from respiratory infections show vaginal discharges. Smears of these discharges show many gram-negative cocci which are not gonococci, but which may be mistaken for them. On certain occasions, smears have been found to be particularly difficult to read when the predominating organism on culture was the streptococcus. Because of these difficulties, diagnosis should be based on culture as well as smear.

Older methods of local treatment of gonococcal vulvovaginitis have been notoriously inadequate. Either the infection persisted in spite of months of treatment, or, as has been reported frequently, many of the so-called cured cases relapsed a few weeks to several months after therapy had been discontinued. Since "cures" were usually based upon smear readings rather than cultures, it is very probable that the continuous presence of the gonococcus—though undetected in smears—accounted for the recurrence of the disease. We had the opportunity to observe the treatment and to study by culture 25 children who received six weeks of local therapy (mercurochrome). Only two (8 per cent) of the group had negative cultures which remained so for one year following therapy. Thirteen of the children had both positive smears and cultures throughout treatment. Ten had periods during and following therapy when the smears were negative although the cultures were persistently positive. This latter group according to older standards of "cure" might have been said to have had recurrences.

In order to evaluate accurately sulfonamide therapy, diagnosis was established by isolation and identification of the organisms before therapy was instituted. To be certain that there would be no recurrence,

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‡The sulfonamides used in this study were furnished through the courtesy of the Medical Research Departments of (1) Winthrop Chemical Company, New York City, (sulfanilamide and sulfathiazole); (2) Merck and Company, Rahway, New Jersey, (sulfapyridine); and (3) Lederle Laboratories, Incorporated, Pearl River, New York, (sulfadiazine).

the determination of cure was based upon cultures and smears taken during treatment, and at regular intervals for one year following the termination of therapy. Such a long period of observation is almost impossible as a practical procedure, but in this study 125 children have fulfilled this strict criterion of cure.

Over 200 children were treated with the various sulfonamides: sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. Forty-five had been deleted because they became delinquent and a full year of observation was impossible. At the time this study was necessarily discontinued, 30 children had ben observed more than three months but less than six months. These cases, too, have been deleted. Ten children who had been observed for more than six months have been included; thus, in Table I, a total of 135 children who had 196 courses of treatment are considered in detail.

TABLE I. NUMBER OF PATIENTS AND COURSES OF THERAPY RECEIVED WHO WERE OBSERVED OVER ONE YEAR AFTER CESSATION OF THERAPY

NUMBER OF PATIENTS			NUMBER OF COURSES
99	One course of treatment		99
36	More than one course of treatment		97
22	2 courses of treatment	44	
9	3 courses of treatment	27	
1	4 courses of treatment	4	
2	5 courses of treatment	10	
2	6 courses of treatment	12	
Total 135			196

All of the children were ambulatory, and most of them were Negroes. They varied in ages from 11 months to 13 years; 20 were under 2 years of age, 54 under 5 years. Three of the girls had their first menstrual period during the year of observation. Eight patients had chronic infections, which had been treated previously by local therapy for varying lengths of time. All the other cases were in the acute stage.

Nine of the children became reinfected during observation and were retreated, and 20 children failed to respond to one or more of the drugs.

When this study was begun, only sulfanilamide and sulfapyridine were available. We expected to treat an equal number of children selected as impartially as possible with the two drugs. It soon became apparent, however, that sulfanilamide was not only not as efficacious in the treatment as sulfapyridine, but that it also produced "drug-fast" gonococcal strains which failed to respond to the other sulfonamides. For that reason, sulfanilamide was discontinued early. When sulfathiazole and sulfadiazine became available, these drugs were included in the study. As the use of sulfonamide therapy in gonococcal infections in both adults and children became more general, it was our observation that the number of new infections in children rapidly diminished. As a result, there were fewer cases for evaluation of sulfadiazine therapy. When the study was discontinued, 35 children had received sulfadiazine. Four of them had failed to respond to the drug or had recurrences after therapy had been discontinued, and only four had been observed over a year. Twenty-two had been observed three months, however, and were probably cured. They are included in the Tables IV and V, merely for comparison with the other drugs.

Table II lists each of the drugs in relation to the number of patients

TABLE II. NUMBER OF PATIENTS TREATED WITH EACH DRUG AND THE TOTAL NUMBER OF COURSES OF EACH DRUG GIVEN—ALL WERE OBSERVED FOR ONE YEAR AFTER THERAPY WAS STOPPED

DRUG	NUMBER OF PATIENTS			NUMBER OF COURSES	
	ONE DRUG	TWO OR MORE DRUGS	TOTAL	SAME DRUG REPEATED	TOTAL
Sulfanilamide	6	12	18	4	22
Sulfapyridine	42	19	61	9	70
Sulfathiazole	63	16	79	14	93
Sulfadiazine	2	2	4	0	4
Stilbestrol		6	6	1	7
Total	113	55	168	28	196

113	patients received 1 drug	113	
22	15 patients received 2 drugs	30	55
	3 patients received 3 drugs	9	
	4 patients received 4 drugs	16	
Total	135	168	

who have been observed for one year. One hundred thirteen were cured by one or more courses of a single drug. Seven patients were reinfected twice. They were retreated with the same or a different drug and observed a full year after the time of reinfection before being discharged as cured. Ordinarily, if a child failed to respond to one drug, a different drug was used for the second course of treatment. Twenty-two patients received more than one drug, 15 received two drugs, three received 3 drugs and four received 4 drugs. When two or three sulfonamides failed to effect cure as was the case with a few children who received sulfanilamide, stilbestrol was tried finally. Since one child could receive one to five different drugs, the total of the numbers of patients on each of the drugs was 168. Occasionally, when a different drug was not available, a child received more than one course of the same drug. Thus, six children responded to a second course and two to a third course of the same drug. In all, the 135 children received 196 courses of the same or different drugs.

Methods

Diagnosis.—Diagnosis in every case was based on isolation and identification of the gonococcus by cultural methods.

Collection of Material for Bacteriologic Examination.—All the children were examined with a vaginoscope and materials for examination collected on two swabs. One swab was used for making the two smears. One smear was examined by the laboratory at the Municipal Social Hygiene Clinic, and the other at the laboratory at the Department of Obstetrics and Gynecology, University of Chicago, using Burke's modification of Gram's stain. The second swab was moistened with a few drops of nutrient broth and used immediately for inoculation of various special media. McLeod's chocolate agar gave the best results of the various media tried. Our procedure has been outlined in detail elsewhere.[3] The inoculated plates were left at room temperature not longer than 5 hours, when they were transported to the laboratory where they were incubated at 35° C. in an atmosphere of 10 per cent carbon dioxide. Plates were examined at 24-hour intervals and discarded after 72 hours' incubation. Tetramethyl-p-phenylene diamine hydrochloride was preferred for the oxidase test. Oxidase positive or suspected colonies (very occasionally certain colonies did not give a definite positive oxidase test on primary isolation) were stained and examined microscopically. The organism was finally differentiated by carbohydrate fermentation.

Treatment and Criteria of Cure.—In Table III, the dosages of sulfonamides and stilbestrol are given. Treatment was withheld until the di-

TABLE III. SULFONAMIDE AND STILBESTROL DOSAGE IN GONOCOCCAL INFECTION IN AMBULATORY CHILDREN

AGE	WEIGHT	DAILY DOSE	NO. DOSES PER DAY	TOTAL DAYS	TOTAL DOSE
		Sulfanilamide			
1 to 2 years	20 to 27 pounds	1.3 Gm. (20 gr.)	4	10	13.0 Gm.
2 to 5 years	27 to 42 pounds	2.0 Gm. (30 gr.)	4	10	20.0 Gm.
5 to 9 years	42 to 62 pounds	2.6 Gm. (40 gr.)	4	10	26.0 Gm.
9 to 11 years	62 to 100 pounds	3.0 Gm. (45 gr.)	4	10	30.0 Gm.
		Sulfapyridine, Sulfathiazole and Sulfadiazine			
1 to 2 years	20 to 27 pounds	0.75 Gm. (11.3 gr.)	4	10	7.5 Gm.
2 to 5 years	27 to 42 pounds	1.5 Gm. (22.5 gr.)	4	10	15.0 Gm.
5 to 9 years	42 to 62 pounds	2.0 Gm. (30.0 gr.)	4	10	20.0 Gm.
9 to 11 years	62 to 100 pounds	2.5 Gm. (37.5 gr.)	4	10	25.0 Gm.
		Stilbestrol			
All ages		0.3 mg. (0.45 gr.)	3	13 to 20	3.9 to 6.0 mg. (5.8 to 9.0 gr.)

agnosis was established by isolation of the gonococcus. Hemoglobin determinations (earlier the carbon monoxide method and later the Dare) were made before and during therapy. Smears and cultures, vaginal pH and blood for determination of drug concentrations were taken twice a week during treatment. Smears and cultures were continued twice a week for three months after therapy had been discontinued, and once a month thereafter, until the patient had negative cultures for one year. No provocative test was used. Marshall's method was used for determination of the concentration of sulfonamide in the blood.

Four doses of drug were given per day, and 10 days constituted a course of treatment. If a patient failed to respond to one course of therapy, a second course of the same drug was occasionally tried, but usually a different sulfonamide was used. Three days usually intervened between courses of treatment in order to allow time for reading the culture taken at the end of the first course of therapy. If a patient failed to respond after 2 or more courses of sulfonamides, stilbestrol was used. After sulfanilamide was discontinued, only one such case was encountered.

Results

Sulfonamide Therapy.—A comparison of the results obtained with the various sulfonamides is made in Table IV. Failures are considered from the standpoint of the particular drug or drugs that failed to effect cure. Although a patient may have required repeated courses of the same drug to bring about cure, the drug was considered to be successful and the previous course or courses of treatment were not listed as failures. Likewise, if a patient failed to respond to repeated courses of the same therapy, but was subsequently cured on another drug, the first treatment was considered to constitute one drug failure even though

TABLE IV. RESULTS OF SULFONAMIDE AND STILBESTROL THERAPY—THE NUMBER OF PATIENTS WHO RECEIVED ONE OR MORE DRUGS

DRUGS	NO. PATIENTS	NO. CURED	% CURED	NO. FAILURES	% FAILURES
Sulfanilamide	18	7†	39	11	61
Sulfapyridine	61	54‡	89	7	11
Sulfathiazole	79	70§	89	9	11
Stilbestrol	6	5	83	1	17
Sulfadiazine*	35	31	89	4	11

*Two observed one year, 33 observed for three months.
†Two patients required 2 courses.
‡One patient required 2 courses and 1 patient 3 courses.
§Three patients required 2 courses and 1 patient 3 courses.

repeated courses of the drug may have been used. Little emphasis should be placed on these cases, however, since it is impossible to be certain whether cure was due to the drug or to the self-limiting course of the infection.

If a patient became delinquent during or just following therapy while the cultures were still positive, the treatment was included as a failure even though the patient had not been observed long enough to effect a cure by other therapy.

Since some patients failed to respond to 2, 3 or 4 drugs, one patient could constitute a failure of 1, 2, 3 or 4 drugs. By this method of tabulation, the total numbers of failures resulting with any one drug could be determined. This might, however, lead to erroneous conclusions if the first drug selected for treatment caused the microorganism to become resistant to all subsequent sulfonamide therapy, as we believe was the case with sulfanilamide. In order to avoid such a fallacy, the first drug which failed to effect cure has been used as the basis for tabulation in Table V. Thus, each patient constituted one drug failure and that failure was credited to the initial therapy. The true figures lie probably some place between these two extremes.

In Table VI, the failures are considered individually. The complete treatment given in each case is listed and the time when cultures were

TABLE V. RESULTS OF SULFONAMIDE THERAPY WHEN ONLY INITIAL FAILURES ARE CONSIDERED

DRUGS	NO. PATIENTS	INITIAL FAILURES	% FAILURES
Sulfanilamide	18	11	61
Sulfapyridine	61	3	5
Sulfathiazole	79	5	6
Sulfadiazine*	35	2	6

*Two observed one year, 33 for three months.

TABLE VI. TREATMENT RECEIVED BY PATIENTS WHO WERE RESISTANT TO ONE OR MORE OF THE SULFONAMIDES

NO. PATIENTS	AGE YEARS	CULTURES +	THERAPY	RESULT
Sulfanilamide Initial Therapy				
520*	4	In 3 days		Delinquent +
356	6	Always	Sp.†	Discharged
385	5	In 3½ months	Sp.	Discharged
559*	1	Always	Sp.	Discharged
367	4	In 1 month	Sp., Sp.	Discharged
390	7	Always	Sp., Sp.	Delinquent +
547	7	Always	St.	Discharged
586	7	Always	S., Sp., St., *Sb.* Discharged	Discharged
589	8	Always	S., Sp., St., St., *Sb.* Discharged	Discharged
593	8	Always	S., Sp., Sp., St., *Sb.* Discharged	Discharged
650	6	Always	Sp., St., *Sb.*, *Sb.*, St. Discharged	Discharged
Sulfapyridine Initial Therapy				
498*	5	In 3 days		Delinquent +
550	2	Always	Sp., St.	Discharged
409*	2	Always	Sp.,St., *Sb.*	Discharged
Sulfathiazole Initial Therapy				
716	8	In 2 months	Sp.	Discharged
741	8	In 2 weeks	Sp.	Discharged
760	3	In 2 weeks	Sp.	Discharged
685	2	Always	Sp., *Sb.*	Discharged
1,561	10	In 3 days	Sd., St.	Discharged
Sulfadiazine Initial Therapy				
1,564	4	In 3 days	St.	Discharged

*Previous local treatment.

†S. — Sulfanilamide, Sp. = Sulfapyridine, St. = Sulfathiazole, Sd. = Sulfadiazine, Sb. = Stilbestrol.

positive during or following treatment is stated. Those patients who failed to respond to therapy and whose cultures remained positive during the treatment period are designated in the column of "cultures +" as "always." This, of course, refers only to the drugs which did not effect cure and not to the final course of treatment. If a patient became negative during treatment, but later relapsed, the interval between positive cultures is given. The individual ages are indicated. The infection was ultimately eliminated in all patients who continued under treatment.

Discussion

In the treatment of gonococcal vulvovaginitis, there seems to be little choice between sulfapyridine, sulfathiazole or sulfadiazine either on the basis of initial or total failures. Response was almost identical: 89 per cent of cure in each series. Sulfanilamide is definitely contraindicated in the treatment of children, not only because it results in a greater percentage of failures (61 per cent), but also because it tends to produce strains of gonococci that are resistant to subsequent sulfonamide therapy. Both sulfanilamide and sulfapyridine produced more minor toxic symptoms than did sulfathiazole or sulfadiazine. Not once were severe toxic symptoms encountered in any of the series.

Stilbestrol was used with some measure of success in a few of the drug-resistant cases, but such cases should be rare when properly selected sulfonamide therapy is used. Five of the six children treated with stilbestrol did become negative during therapy and remained so. The sixth case responded to a combination of sulfathiazole and stilbestrol therapy. All the children that received stilbestrol showed some evidence of secondary sexual changes, but these regressed within a month after therapy had been discontinued. One such case has been described by us in detail elsewhere.[2]

There was considerable difficulty in determining whether some of the children had been reinfected or had a recurrence. If the child was known to have had contact with a member of the family or a playmate who had the infection, we were inclined to consider the possibility of reinfection, particularly if the cultures had become negative previously during treatment. Where no such contact was known, the treatment was considered a failure. We consider cultures taken during therapy to be most useful in evaluation of therapy. Ninety-five per cent of the patients that responded to one course of therapy had negative cultures three days after starting the therapy, whereas 65 per cent of the failures had positive cultures throughout treatment or did not become negative on culture until six to nine days after therapy was begun.

Of the 20 children considered failures on sulfonamide therapy, 11 had positive cultures throughout the courses of treatment. Of the nine who had negative cultures during treatment and later relapsed, six had positive cultures within two weeks after therapy was discontinued, one in a month, two within two months and one in three and one-half months. One child had a positive culture on the day she was to have been discharged after a year of observation. It was difficult to know whether this was a reinfection or a drug failure. No evidence of contact could be elicited. She was retreated with the same drug, and discharged cured a year later.

As a practical procedure, three months is probably long enough to observe children before they are discharged as cured, provided the diagnosis of cure is based on appropriate cultural studies. Patients under treatment and observation may be permitted to return to school as soon as cultures have become negative.

Although children require proportionately larger doses of drug and longer courses of therapy than do adults, young children responded to therapy as well as did the older ones. Of the 135 children studied, 54 were under 5, and 81 were over 5 years of age. Seventeen per cent of the children under 5, and 14 per cent of the children over 5 made up the group of "drug-failures."

Chronic infections did not respond to sulfonamide therapy as well as did acute cases. Eight children had chronic infections which had been treated previously with local therapy. Four of them (50 per cent) failed to respond to one or more courses of sulfonamides.

Hemoglobin determinations made before therapy was instituted showed variations from 56 to 98 per cent. Only 19 (14 per cent) of the children were below 70 per cent, and only one of the failures was in this group.

Determinations of concentrations of the drugs in the blood during therapy showed levels varying from a trace to 8.0 mg. per hundred cubic centimeters. The children that failed to respond to therapy did not have uniformly lower blood levels, than those that were cured by one course of treatment.

Conclusions

1. Diagnosis and criteria of cure of gonococcal vulvovaginitis should be based on cultures as well as smears.

2. Sulfathiazole and sulfadiazine are the drugs of choice in the treatment of this infection. Of 135 children treated with sulfanilamide, sulfapyridine or sulfathiazole and observed one year following therapy, equally good results were obtained with sulfapyridine and sulfathiazole whether response was based on cure (both 89 per cent), or upon initial failure (sulfapyridine 5 per cent, sulfathiazole 6 per cent). Sulfapyridine caused more minor toxic symptoms than did sulfathiazole. Sulfanilamide is definitely contraindicated because of the higher percentages of failures and because it tends to produce strains of gonococci which are resistant to sulfonamides. Of 35 children treated with sulfadiazine and observed three months following therapy, 89 per cent were cured and 6 per cent were initial failures.

3. Stilbestrol was useful in the treatment of sulfonamide-resistant cases.

4. Negative cultures for three months are probably sufficient criteria to establish a cure.

5. Patients under treatment and observation may be permitted to return to school as soon as cultures have become negative.

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CRANIOTOMY*

With Review of Cases

J. Irving Kushner, M.D., F.A.C.S., and A. Charles Posner, M.D., F.A.C.S., New York, N. Y.

(From the Obstetric Service of The Bronx Hospital, New York, N. Y.)

CRANIOTOMY is one of the most serious obstetric operations. Very little is written concerning its indications and technique. Frequently it is not used when it should be. Because it is gruesome and a mutilating procedure, few authors write in great detail on this important subject.

Too often have women, who give a history of premature rupture of the membranes, long hours of labor, and either repeated vaginal examinations or attempts at delivery, or both, been subjected to cesarean section with the delivery of a dead baby. Frequently, in order to save the lives of these women, a radical operation with removal of the uterus is done, thereby destroying the possibility of future childbearing. Many mothers have undergone the dangers of cesarean section to have presented to them a hydrocephalic child, or a child so damaged that it does not survive or, at best, is mentally deficient.

Craniotomy should be performed whenever the child is dead, unless it may easily be delivered by forceps. It should be done on hydrocephalic children where there is marked disproportion, or in other types of maldevelopment, provided the diagnosis is confirmed beyond a shadow of doubt and the mother cannot be delivered per vaginam. Craniotomy should not be done if the conjugata vera is below 6.5 cm., or where the pelvic canal is blocked by ovarian or uterine tumors, or when the cervix is fibrous or carcinomatous.

Incidence.—In this series of cases, from July, 1932, through June, 1943, at the Bronx Hospital, there were 22,705 deliveries. Of this number, 19 were delivered by craniotomy, a percentage of 0.084. (Table I.) Bailey and Williamson[1] reported 3 craniotomies out of 11,491 deliveries, a percentage of 0.026. Good[2] reported 8 craniotomies out of a total of 22,674 deliveries, a percentage of 0.36. Long and Stabnick[3] report 29 craniotomies out of 12,292 deliveries, a percentage of 0.235.

*Read before The Bronx Gynecological and Obstetrical Society, Nov. 27, 1944.

Indications.—The indications for the craniotomies in this series are presented in Table II. It can be seen that cephalopelvic disproportion with a dead fetus was found in six cases. In one of these cases the disproportion was unrecognized and an attempt at forceps delivery having failed, a craniotomy was done. In two cases with a recognized flat pelvis, attempts at manual dilatation of the cervix resulted in a dead baby. One

TABLE I—SUMMARY OF THE CASES

CASE NO.	HOSP. NO.	AGE (YEARS)	GRAVIDA	PARA	PELVIC TYPE	HOURS OF LABOR			INDICATIONS FOR ORIGINAL OPERATION						INDICATIONS FOR CRANIOTOMY						
						1ST STAGE	2ND STAGE	RUPT. MEMB.	FETAL DISTRESS	PERSISTENT OCCIPITOPOSTERIOR	PRE-ECLAMPSIA	CERVICAL DYSTOCIA	INTRAPARTUM INFECTION	FAILURE OF FORCEPS	DEAD BABY	BANDL'S RING	PROLAPSED CORD	CEPHALOPELVIC DISPROPORTION
1	143474*	30	ii	i	Normal	39	1½	39	x			x		x	x			x
2	142531	24	i	0	Normal	31	8¼	26	x	x				x	x	x		
3	132538	37	iii	0	Normal	104	3¾	30	x	x	x			x	x			
4	92709	27	iii	i	Normal	60	¼	20						x	x			x
5	65214	21	i	0		36			Manual dilatation at home						x			Hydrocephalus
6	63471*	22	i	0	Normal	72	3	30		x			x		x	x		x
7	63338	31	i	0	Android	10	5	15		x				x	x			
8	44945	30	ii	0	Android	55	4	40		x				x	x			
9	39619	30	ii	0	Flat	12		10						x	x			
10	134316	28	i	0	Flat	30½	2¼	22							x†		x	
11	120323	24	ii	0	Normal	23½	8	7	Intrauterine death for 68 days									
12	128470	26	ii	i	Normal	6	3	4	Ineffectual labor pains					x	x	x		
13	117471	26	i	0	Normal	10½	4½	4		x								x
14	118007	40	v	ii	Normal	9½	1¼	8	Bag induction—attempts at high forceps					x	x	x		Hydrocephalus
15	98449	21	i	0	Normal	67	¼	67						x	x		x	x
16	77717	21	i	0	Normal	98	1	40										Hydrocephalus
17	57931	24	i	0	Flat	42				x								x
18	51804	35	i	0	Flat	40	¼	39							x†		x	Hydrocephalus
19	41009	24	i	0	Normal	60		64							x			

*Maternal death.
†Unengaged vertex.

TABLE II—INDICATIONS FOR CRANIOTOMY

INDICATIONS	NO. OF CASES	MATERNAL RECOVERY	END RESULT DEATH
Unrecognized cephalopelvic disproportion; attempted forceps; dead fetus	1		1
Flat pelvis; cephalopelvic disproportion; attempted manual dilatation; dead fetus	2	2	
Flat pelvis; cephalopelvic disproportion; prolapsed cord; dead fetus	3	3	
Attempted forceps for occipitoposterior; Bandl's ring; dead fetus	4*	3	1
Attempted forceps for occipitoposterior; dead fetus	3	3	
Hydrocephalus; disproportion	4	4	
Intrauterine death for 68 days; ineffectual labor pains; dead baby	1	1	
Bag induction for cervical dystocia; dead fetus	1	1	

*Version was also attempted in two cases, following failure of the forceps and before craniotomy was done.

of these was performed at home, and in the other, a craniotomy in the hospital gave rise to a rupture of the lower uterine segment. Prompt hysterectomy with the recovery of the mother occurred. In the other three cases, prolapse of the cord caused fetal death, and a craniotomy was the delivery of choice.

In seven cases forceps failed to deliver a baby which was in an occipitoposterior position, with a subsequent loss of the fetal heart. In four of these cases in the presence of a Bandl's ring the dead fetus was delivered by craniotomy under profound anesthesia. In the other three cases while there was no Bandl's ring, craniotomy was resorted to, version being contraindicated because of a tight uterus due to the length of time the membranes had been ruptured.

In our series, hydrocephalus occurred four times. In each case the diagnosis was confirmed by x-ray and a craniotomy was done because of the marked disproportion.

There was one case of fetal intrauterine death for 68 days with ineffectual labor pains, and one case of bag induction for cervical dystocia with the loss of the fetal heart at about five fingers' dilatation.

Length of Labor.—The length of labor of this group of patients varied between 107 and 9 hours. All of our cases had a history of early rupture of the membranes, the longest being 67 hours.

Maternal Mortality.—In this series of cases there were two maternal deaths, a percentage of 10.5. The details of these cases are shown in Table III.

TABLE III. MATERNAL MORTALITY

CASE NO.	INDICATIONS FOR CRANIOTOMY	CAUSE OF DEATH
143474	Failure of forceps for occipitoposterior; cephalopelvic disproportion; dead fetus	? Acute renal cortical necrosis
63471	Failure of forceps for occipitoposterior; Bandl's ring; dead fetus; intrapartum infection	Septic pelvic thrombophlebitis

Patient No. 143474, aged 33 years, gravida ii, para i. Membranes ruptured 39 hours, total labor 39½ hours, second stage 1½ hours. Intrapartum eclampsia. Craniotomy was done because of the failure of forceps to deliver an occipitoposterior with subsequent loss of the fetal heart. A congenital oxycephaly was delivered. The patient expired on the tenth postpartum day with signs which were interpreted by the medical consultant as being due to acute renal cortical necrosis.

Patient No. 63471, aged 22 years, primigravida. Total labor 72 hours, second stage, 3 hours, membranes ruptured 75 hours. Intrapartum infection. Failure of forceps for occipitoposterior. With the loss of

fetal heart, craniotomy was done. Patient ran a septic course due to a pelvic thrombophlebitis and expired on nineteenth postoperative day.

Technique.—A few words about the technique of craniotomy will not be amiss. In view of the shock, the patient should be typed and compatible blood should be ready for a possible transfusion. The procedure must be done under general anesthesia. Spinal anesthesia or caudal analgesia are definitely contraindicated. The patient should be redraped and have a new vaginal preparation. Catheterization should be done before and after the operation to make sure that there has been no bladder injury. The procedure following the original description of Tarnier* should be strictly adhered to. After the delivery of the fetus, the placenta should be removed manually in order to save blood loss and to explore the uterus for possible rupture. This should be followed by a uterine packing. Chemotherapy should be started immediately.

Summary

Out of 22,705 deliveries at the Bronx Hospital, 19 were delivered by craniotomy, a percentage of 0.084. In these 19 cases there were two deaths, a percentage of 10.5.

Conclusion

1. Craniotomy is a necessary obstetric operation.
2. It is safer for the mother with a dead baby that cannot be delivered by forceps or version, or for the mother who is obviously infected.
3. It is the operation of choice for the delivery of malformations where vaginal delivery is difficult or impossible.

We are indebted to Meyer Rosensohn, M.D., F.A.C.S., Attending Obstetrician, The Bronx Hospital, for his helpful suggestions in the preparation of this report.

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1840 Grand Concourse
51 East 90th Street

*Bull. Acad. de med., Paris, 12: 1425, 1883.

ESSENTIAL DYSMENORRHEA—ITS TREATMENT WITH PAVATRINE*

A Preliminary Report

C. H. Weinberg, M.D., New Orleans, La.

AS NUMEROUS as are the theories of dysmenorrhea, the proposed medications are even more numerous.

It follows, of course, that since we are still ignorant as to the true cause of dysmenorrhea in the absence of pelvic pathology, and as dysmenorrhea is a symptom and not a disease, no one routine of treatment regularly gives any measure of success. For the most part, also, it is usually not possible to differentiate in any one individual the type

*B-diethylaminoethyl fluorine-9-carboxylate hydrochloride (Pavatrine). Supplied by G. D. Searle & Co.

of dysmenorrhea present, and there is always overlapping of the classified types: (a) the neurotic, (b) the obstructive, (c) the hypoplastic, and (d) the constitutional.

After many false starts, the author has had such improved results with the technique outlined below, that he feels that his findings are worthy of note.

It is freely admitted that pain is an individual concept; that the threshold of pain varies greatly, and that results are often untrustworthy when based on a history of symptomatic relief. In a later paper an attempt will be made to present scientific proof of the comparative value of antispasmodic drugs by means of a new type of apparatus now under construction. At present the findings are based upon symptomatic relief.

Method of Study

In the general series, patients were divided into two classes: (a) those whose chief complaint was menstrual cramps, and (b) those who, in the course of a routine gynecologic history, stated that menstrual pains were severe enough to cause them to alter their usual routine—either by remaining home from work and/or by making it necessary for them to remain in bed on the day or part of the day that their periods began.

In the present series, 141 cases have been reviewed. Of these, 41 could be explained on the basis of outstanding pathology that required operative correction or treatment, and are not included in the series.

Twenty cases complained primarily of painful menstruation, and these are divided into groups as shown in Table I.

Of those whose chief complaint was not painful periods, but who nevertheless suffered from severe enough pain to alter their usual activities, the division of cases is as shown in Table II.

TABLE I. CHIEF COMPLAINT—PAINFUL PERIODS

Single	8	Married	12
Average age	19	Average age	29
Disability:		Disability:	
Complete	3 (37%)	Complete	3 (25%)
Partial	5 (63%)	Partial	9 (75%)
Relief:		Relief:	
+++ to ++++	6 (75%)	+++ to ++++	8 (66+%)
+ to ++	2 (25%)	+ to ++	4 (33+%)

+++ and ++++ represent: no alteration in usual routine.
+ and ++ represent: relief, but some incapacity remained.

TABLE II. CHIEF COMPLAINT—OTHER GYNECOLOGIC SYMPTOMS

Single	0	Married	80
		Average age	33
		Disability:	
		Complete	16 (20%)
		Partial	64 (80%)
		Relief:	
		+++ to ++++	53 (66%)
		+ to ++	27 (34%)

For key to symbols, see Table I.

Method of Dosage and Control of Cases

Since dysmenorrhea cannot always be explained by organic pathology, and since the psychic effect of any "new medicine" is unquestionably great, it is necessary in any series to check each result carefully. Where a large group can be used at one time and placebos

substituted in a portion of the cases, control is easily enough established, but in private practice, where it is always necessary to furnish relief, this method is impractical. Therefore study was carried out in the following manner:

Each patient was given a prescription for pavatrine and instructed to take one tablet three times a day after meals, beginning three days before the onset of the expected period, and likewise on the first day of the period. If the period was delayed one or two days, the medication was to be continued in like manner, but no patient took pavatrine more than five days before the periods began.

Each patient was also given a second prescription for capsules, each containing phenobarbital ½ grain, extract hyoscyamus ⅚ grain, and amidopyrine 5 grains. She was told that this was an "emergency" drug and was instructed that she was not to use it unless her cramps were not relieved, but if her cramps were painful and she could not go about her usual activities, she was to take one capsule every four hours, as long as she remained uncomfortable. In this way an estimate of the amount of relief obtained by the pavatrine alone could be made, for if it was not necessary to take any of the capsules, then results were considered excellent. If, however, three or more capsules were necessary in any twenty-four hours, then obviously the pavatrine was of no measurable value.

No case is recorded in which this study does not cover a minimum of six menstrual periods, and as further check, one-half of the cases who responded well to pavatrine were asked to omit it for one month. In this latter group, there was return of their dysmenorrhea in every case.

In Table III the results in the series are demonstrated.

TABLE III. BREAKDOWN OF SERIES

Number of Cases:	100
1. Number with complete relief	48 (48%)
2. Number in which one capsule occasionally necessary	19 (19%)
3. Number in which two capsules necessary	23 (23%)
4. Number in which three+ capsules necessary (Failures)	10 (10%)
Therefore, relief (1 + 2)	67%

Rationale of Treatment

The etiology of dysmenorrhea is itself unknown. It is not the purpose of this paper to review the numerous theories as to the cause of dysmenorrhea. For our purposes, suffice it to say that the pain is certainly related to the uterine musculature or its innervation or both.

Pavatrine possesses both musculotropic and neurotropic action. Its action simulates that of morphine, but it has the marked advantage of being nonnarcotic.

Bickers[1] has demonstrated its antispasmodic effect and found it superior to other antispasmodic drugs. His method, however, employing the intrauterine balloon, involves the introduction of a foreign body into the uterus. In spite of the fact that a foreign body tends to increase the irritability of the uterus, unquestionably pavatrine, in this series, reduced the uterine contractions to a far greater extent than the other drugs investigated, with the exception of morphine.

Untoward Effects

Three of the cases were failures because of an apparent idiosyncrasy to the drug. This consisted of a severe trembling of the hands and a complete feeling of inability to control locomotion. As one patient expressed it, she felt as though she was "literally falling apart."

This sensation is unquestionably due to the marked relaxing effect of the drug. In such patients it should, of course, be discontinued.

Disadvantages

The drug should be begun a minimum of three days before the onset of the menstrual period. In irregular cycles the period will often present itself before any of the drug has been taken. In these cases the drug may be taken with the onset of the period, but it has been my experience that under these circumstances it loses much of its efficiency. On the other hand I have seen no harm in beginning medication too early. Patients may take pavatrine continuously for five days or more before the onset of the period without apparent side effects.

Selected Case Reports

Typical Successful Response.—Mrs. S. A., aged 23 years. Dysmenorrhea since menarche at 14 years of age. Periods regular. One child, aged 3 years. No relief from dysmenorrhea except during pregnancy and for first three months thereafter. With re-establishment of periods, menstrual "cramps" began.

Tried proprietary remedies and prescriptions by several doctors without relief.

No organic pathology present.

Placed on pavatrine, one tablet three times a day after meals, beginning three days before expected period. Complete relief for three months, then period began four days early. Took pavatrine on day of onset of period with partial relief only. Periods thereafter again regular. Pavatrine has relieved this patient with above exception for period of nine months.

Demonstrating Idiosyncrasy to Pavatrine.—Mrs. H. C., aged 26 years. Menarche at 13 years of age. Periods regular. Dysmenorrhea first day. Married three years, no children. No organic disease demonstrable.

Placed on pavatrine. After second dose became so dizzy that locomotion was impossible. Repeated attempts brought about the same symptom complex. Drug discontinued because of obvious idiosyncrasy.

Typical Failure of Response.—Mrs. C. L., aged 29 years. Two children. Periods regular. Dysmenorrhea since menarche.

Examination showed erosion of cervix, which responded to treatment.

Afterwards placed on pavatrine. First month necessary to take four capsules in twenty-four hours. Second month, slight relief, took two capsules. Third month, no apparent relief. Fourth month, no relief.

This case constitutes a complete failure.

Conclusions

A review of 100 cases of dysmenorrhea treated with pavatrine is presented.

The results seem to warrant that, with proper dosage, pavatrine is highly successful in relieving dysmenorrhea.

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3439 Prytania Street

TEST CASE TO SHOW VALUE OF CERVICAL CYTOLOGY SMEAR IN UTERINE CANCER DIAGNOSIS*

J. Ernest Ayre, M.D., W. A. G. Bauld, M.D., and P. J. Kearns, M.D.
Montreal, Quebec
(From the Department of Obstetrics and Gynecology, Royal Victoria Hospital, McGill University)

CERVICAL cytology smears have been found to detect uterine cancer in lesions so minute as to be missed by the examining finger, the eye, or even the biopsy knife. Such a statement seems fantastic at first, and yet the illustrations accompanying this article prove it is not impossible. The explanation lies in the fact that any cancer lesion large enough to cause "spotting" desquamates specific cancer cells which appear in the blood and discharge, gathering at the external cervical os, to be spilled down into the vaginal secretions below.

Papanicolaou and Traut[1] were the first to describe specific cancer cells in the vaginal secretions of uterine malignancies. Meigs[2] corroborated their findings, confirming the high degree of accuracy described by the original investigators. Both groups admitted that the search for cancer cells was arduous and prolonged in some cases, at times requiring a study of three separate smears to arrive at the correct diagnosis. One of us (J. E. A.)[3] has recently described a modification of the technique whereby smears taken routinely from the external cervical os showed larger concentrations of cancer cells. The search for the diagnostic cancer cells was, therefore, facilitated and accelerated, rendering the test more efficient.

The cytology of smears prepared from the cervical os is different from that found in the vaginal smear. This is true of normal cases as well as in cancer. In the normal cases, larger numbers of cervical cells, squamous and glandular, and of the endometrial cells from above are found in the secretions at the cervical portal. Most cancer of the genital tract arises from either the cervix or the fundus uteri. Therefore, it seems only natural that larger concentrations of the telltale malignant cells may be found at the external os, the source of the spill. Therefore, small early growths manifesting only occasional desquamation and spotting, which may require prolonged study for diagnosis by the vaginal smear, yield a more speedy decision in the rapid detection of cancer cells in the cervical cytology smear. While three slides may be required to diagnose some cases by the vaginal smear one is usually sufficient in the cervical cytology smear.

Case Report

The patient, a 42-year-old American woman, was admitted to the Women's Pavilion of the Royal Victoria Hospital on April 9, 1944. She gave a history of having been delivered of a child by instruments eighteen months previously. A year later a checkup revealed a small erosion from which a biopsy was taken by her physician in New York

*Aided by a grant from the Banting Research Foundation.

State. The biopsy was reported as showing a cervical malignancy, and the patient was referred to Dr. W. A. G. Bauld, head of the Cancer Clinic of the Women's Pavilion. Pelvic examination, on admission, revealed a moderately enlarged mobile uterus attached to a hypertrophic, freely movable cervix. Dr. Bauld stated at this time that he could find no cervical lesion demonstrable clinically, other than the usual small circular erosion about the external os. Cervical cytology smears were taken and studied. The first smear was reported positive for cancer. On the basis of the smear findings, coupled with the history of the cervical biopsy, a panhysterectomy was performed.*

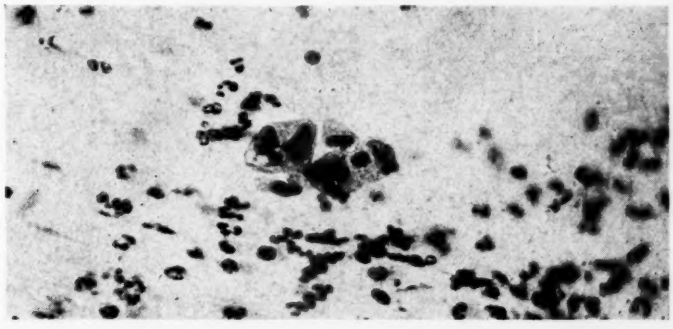

Fig. 1.—Showing cells found in cervical os smear. Note variable size and conformation of nuclei, also some vacuolation in cancer cells.

Pathologic Report.—Grossly the specimen consisted of a generally enlarged uterus with cervix attached, measuring 18 by 13 by 8 cm. The cervix appeared hypertrophic with a small circular eroded area surrounding the external os. Repeated sections of the cervix showed no ulcerated or indurated portion. In view of the suspicion of cancer aroused by the history and the vaginal smear findings, four separate cervical biopsies were taken at 12, 3, 6, and 9 o'clock, respectively. None of these exhibited any gross evidence of cancer. The other organs showed no relevant disease.

The microscopic findings were of interest. The first segment of cervix examined showed evidence of cystic cervicitis with a normal appearing squamocolumnar junction (Fig. 2). The second segment examined, however, showed a different picture. The squamous epithelium appeared normal up to a point approaching the squamocolumnar area. Here the character of the squamous eqithelium exhibited a distinct and abrupt change, the epithelium becoming thicker and the cells showing an hyperplastic appearance. The cytology of this area exhibited a tendency to immaturity, the cells presenting many large and numerous small pyknotic nuclei. Some of these showed evidence of mitosis. There was no marked invasion of the cervical stoma, but the subepithelial tissues in the hyperplastic zone showed a definite round-cell infiltration (Fig. 3).

The other pelvic tissues showed no evidence of involvement, although the myometrium showed an independent lesion in the nature of a deeply spreading adenomyosis.

Dr. Bauld, in replying to the physician who had referred the patient to him, summarized the case as follows: "Mrs. L. referred by you has been treated by hysterectomy. I confirmed your diagnosis prior to operation by vaginal (cervical) smears which showed definite cancer cells. I could not localize the site of the lesion as the cervix was perfectly healthy in appearance. On this reasoning, I felt that operation would complete the treatment more effectively than radiation. I did a total hysterectomy and bilateral salpingo-oophorectomy. Test of the cervical tissue postoperatively showed a very minute superficial cancerous lesion of the cervix, one of the earliest in our records. I think we can look forward to an almost certain cure."

*We usually make it a practice to confirm smear findings by the biopsy before resorting to operation or radiotherapy.

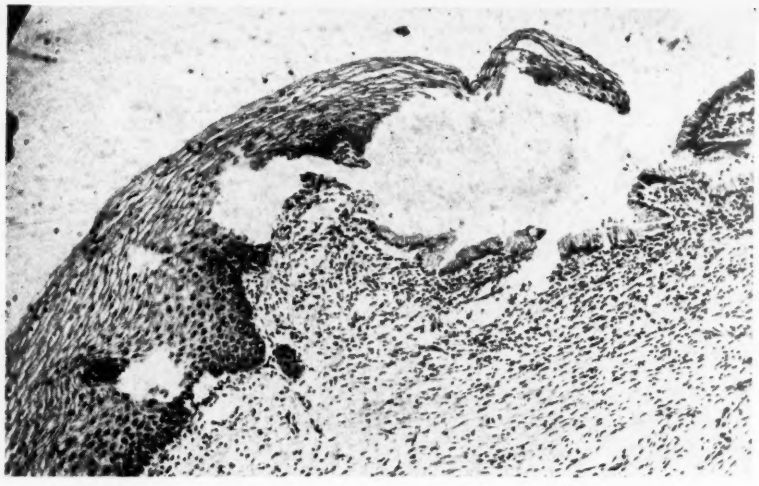

Fig. 2.—First cervical biopsy showing cystic cervicitis with normal appearing squamocolumnar junction.

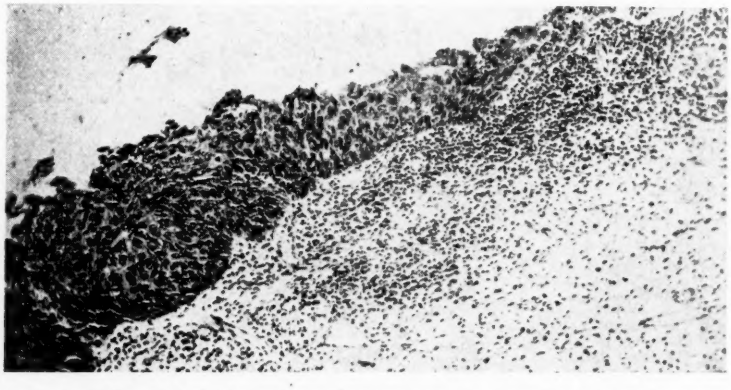

Fig. 3.—Second cervical biopsy showing change in character of squamous epithelium approaching squamocolumnar junction. Note superficial noninvasive cancer (Bowen's disease).

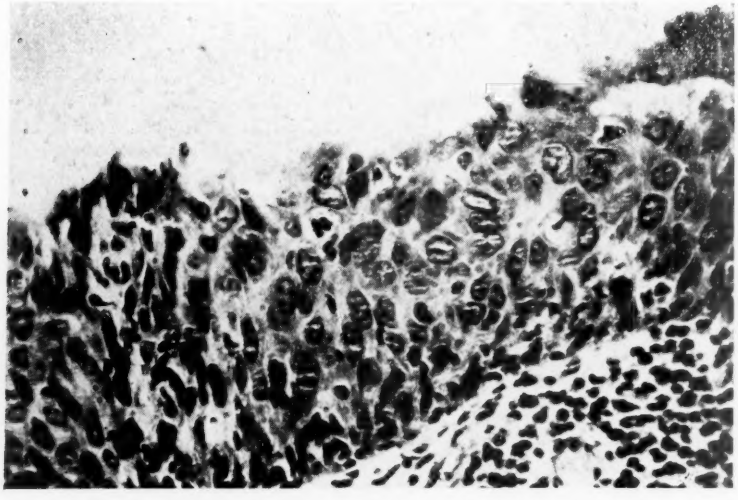

Fig. 4.—High-power photomicrograph of cancerous area. Note resemblance of cells in smear to those along the surface.

Criteria of Diagnosis

Considerable study of normal and abnormal vaginal and cervical cytology is necessary to enable one to accurately differentiate the cancer cell from the benign cell. In general, the criteria as outlined so beautifully by Papanicolaou and Traut in their monograph[4] have been followed. In brief, the finding of blood and pus cells scattered among normal squamous cells with more or less numerous atypical cancer cells showing specific nuclear changes (multilobulation, multinucleation, anisocytosis, pyknosis, and multiple chromatin granulations) is significant.

The morphology of the cancer cells found in different cases is extremely variable. But the cells from any one case are usually found to be similar to the cells found in the actual tissue biopsy in that case (Figs. 1 and 4).

Technique

The technique is that described in "A Simple Office Test for Uterine Cancer Diagnosis."[3] The cervical cytology smear is taken, using a curved glass pipette following exposure with a bivalve speculum. The mucous and blood present at the external os of the cervix or from the surface of the lesion is drawn up into the pipette by suction. This is transferred to a glass slide suitably labeled. The mucus is spread over the slide to prevent the smear being too thick. The slide is then immediately immersed in a solution of ether and alcohol 95 per cent (equal parts). Up to this stage, the test may be taken in the office or clinic, wherever the patient is first seen. The bottle containing the smears is then sent to the cytology laboratory for the more complicated process of staining and expert interpretation.

The simplicity of the test is important, as the inevitable delay associated with an advisement of hospitalization for biopsy is eliminated. Therefore, the case arousing only suspicion of malignant possibilities in the physician's mind is given the benefit of a "surface biopsy" without waiting until signs of more advanced growth indicate that hospitalization and biopsy have become an obvious and imperative conclusion.

Observation

The opinion of the chief gynecologic pathologist (P. J. K.) is that the lesion is an early superficial squamous-cell carcinoma, which at this early stage is still noninvasive. This would appear to fall into the group of early cancer lesions described as "Bowen's disease." Some pathologists have argued that the lesion is not cancer until there is invasion. It is our conception, however, that lesions so early and so minute as this one appears to be should be considered as cancer in a preinvasive form. No doubt if the disease were diagnosed very early more often, it would be found to be in this relatively benign preinvasive stage.

Summary

A case has been presented in which an early cervical cancer was detected by the cervical cytology smears while the lesion was so localized as not to be detectable by the trained eye or the finger, and 50 per cent of the surgical biopsies failed to show it.

It would appear that the vaginal and cervical cytology smears are of definite value in the diagnosis of very early as well as advanced cases of uterine malignancies.

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Drummond Medical Building

PAROVARIAN CYST CAUSING DYSTOCIA

WENDELL DOWNING, M.D., AND LAWRENCE O'TOOLE, M.D., LE MARS, IOWA
(From the Le Mars Clinic)

IN 1939 the authors,[1] in a review of the literature since 1873, reported 62 cases of paravarian cysts complicating pregnancy, seven of which produced dystocia. A personal case was reported in which an intraligamentary cyst resulting in dystocia was treated by aspiration through the vaginal wall, permitting a spontaneous delivery to occur. In 1940 the following almost identical case was encountered.

Case Report

Mrs. A. S., aged 37 years, para vii, admitted to the hospital May 20, 1941, gave the following history: In October, 1939, the patient had had a spontaneous abortion at three months followed by a third-degree retroversion which was corrected by a pessary. After the sixth month of her present pregnancy she had four prenatal examinations. No unusual symptoms or signs were elicited, and a vaginal examination was not made. On Nov. 20, 1940, she was seen at her home in the country by one of us. Labor had been in progress for nine hours. Vaginal examination revealed complete effacement and dilatation but the fetal head did not advance with her pains. A soft fluctuant mass the size of a baseball was palpable in the cul-de-sac on vaginal and rectal examinations. With a syringe and large needle inserted through the posterior vaginal wall in the midline, 150 c.c. of clear fluid was aspirated from the cyst. The head then promptly descended and the patient was delivered of a 10-pound infant. Her puerperium was normal and at eight weeks post partum no pelvic mass was palpable. Surgical removal of the cyst was advised but not agreed to. On May 18, 1941, the patient was again seen in the office with a complaint of pain and left lower quadrant soreness of several days' duration. She also complained of rectal and bladder pressure. Abdominal examination revealed tenderness deep in the left lower quadrant. On vaginal examination a soft tender mass was just palpable to the left and posterior to the uterus. The leucocyte count was 16,000. A diagnosis of a cyst with a twisted pedicle was made and immediate surgery advised. For two days the patient was more comfortable, then the pain again became severe. On admission to the hospital her leucocyte count was 6,000 and her general condition was good.

An exploration through a left paramedian incision showed the uterus to be normal in size and position. A mass, 12 cm. in diameter, was present in the cul-de-sac, being adherent to the peritoneum by fibrinous exudate. The mass was a left parovarian cyst with a narrow pedicle 7 cm. long, twisted two complete turns counterclockwise, the pedicle arising from the left broad ligament just beneath the fimbriated end of the left tube. The thick-walled cyst and pedicle showed hemorrhagic changes; the cyst contained 150 c.c. of serosanguinous fluid. The fimbriated end of the tube was obliterated by fibrous adhesions. The ovaries and right tube were normal. The cyst and left tube were removed and all raw surfaces peritonealized. An appendectomy was also done. The patient made an uneventful recovery and was dismissed from the hospital on the eleventh postoperative day.

Aspiration of a cyst impacted in the pelvis during labor is a safe and simple procedure. Removal of the cyst at an early date is always advisable.

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INTRAPERITONEAL NABOTHIAN CYST

ROBERT T. FRANK, A.M., M.D., NEW YORK, N. Y.

MRS. N. C., aged 22 years, was referred to me because of attacks of right lower abdominal pain, correctly ascribed to slight torsion of the pedicle of a right ovarian cyst.

Examination showed a healthy young woman. The genital tract was nulliparous, uninfected; the uterus anteflexed, of normal size; the right ovary enlarged to orange size, tender; the left adnexa normal. The cervix was normal.

In November, 1943, through a paramedian suprapubic incision an orange-sized bluish thin-walled cyst of the right side was excised and a prophylactic appendectomy performed.

Examination of the field preceding closure revealed a thin-walled colorless cyst projecting above the contour of the uterus on its posterior surface (Fig. 1). The cyst was 3 by 2 by 1 cm. The origin of this cyst puzzled me. At this level, Gartner's cysts are found not in uterine tissue but in the broad ligament. Cysts due to adenomyosis would contain chocolate fluid. Without further speculation, however, the cyst was removed by excising it together with a thin layer of uterine muscle, and the resulting defect was closed by suture. Convalescence was uneventful.

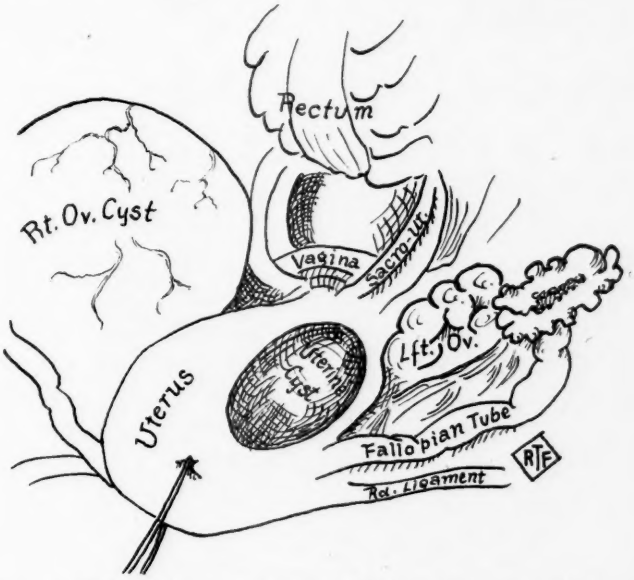

Fig. 1.—Uterus pulled to right exposing nabothian cyst on posterior surface of uterus above sacro-uterine ligaments.

To my surprise the uterine cyst was reported as "cervical tissue with nabothian follicles and chronic inflammation." When I informed Dr. S. Otani, the Associate Pathologist of Mount Sinai Hospital, from what location I had removed the specimen, he too was astounded, but when we reviewed the specimen together, no other interpretation was possible (Fig. 2).

Comment.—The intraperitoneally presenting cyst in the lower posterior uterine wall was due to dilatation of cervical glands which grew and developed outward and upward instead of downward toward the

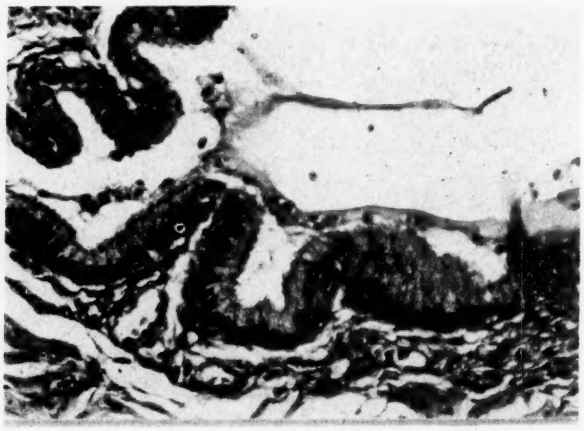

Fig. 2.—Photomicrograph of lining of uterine cyst. Typical cylindrical cervical epithelium.

portio as is usual. The possibility that these glands originally were abnormally located seems likely because I have never previously encountered, nor have I seen any mention in the literature, of a similar localization, in sharp contrast to the great frequency of nabothian cysts of the portio.

AVULSION DEFECTS OF THE SCALP OF THE NEWBORN INFANT

Medicolegal Implications

WILFRED J. FINEGOLD, M.D., AND EUGENE B. SCHUSTER, M.D., PITTSBURGH, PA.
(From the Departments of Obstetrics and Pediatrics, Montefiore Hospital)

THE importance of the recognition of congenital defects of the scalp lies in the fact that they may be mistaken for a result of obstetric trauma. Finkelstein[1] refers to the necessity of a clear differentiation of these congenital defects from traumatic lesions for medicolegal reasons. He cites several lawsuits instituted against obstetricians. Some of the early reports suggest that prenatal trauma is the cause of these scalp defects. Abele[2] considered his case due to an injury sustained by the mother ten weeks before birth, and Schatz[3] attributed his case to an exostosis of the maternal pelvis.

Although these defects can be found on any part of the newborn infant, they are most commonly found on the scalp. The lesions are of comparatively rare occurrence. Rogatz and Davidson,[4] in 1942, found that not more than 125 cases had been reported. In 1930, Terruhn[5] reviewed 76 cases, in which the head was involved in almost half. Abt[6] reported 37 cases up to 1917.

The common type consists of single or multiple pinhead to coin-sized defects of the scalp over one of the parietal bones. They are irregularly oval in shape and have punched-out margins which may present more or less evidence of healing.

Most writers, including Abt,[6] attribute the lesions to inflammatory adhesions between the external layers of the skin and the amnion. As the amniotic

fluid accumulates, the adhesions are put under tension and stretch into the so-called Simonart's bands. When these bands are torn loose from the fetal integument, a defect remains. Because these lesions are consistent with this probable etiology, we choose the term "avulsion defects" to differentiate them from the congenital dysplasias and aplasias of the skin of the newborn infant also commonly referred to as "skin defects."

Abt[6] concluded from microscopic examination that growth of squamous epithelium, smooth muscle, and fat are retarded in the fetal areas involved. The presence of well-developed connective tissue (possible beginning healing?) led him to believe that the defects were caused during early embryonal life.

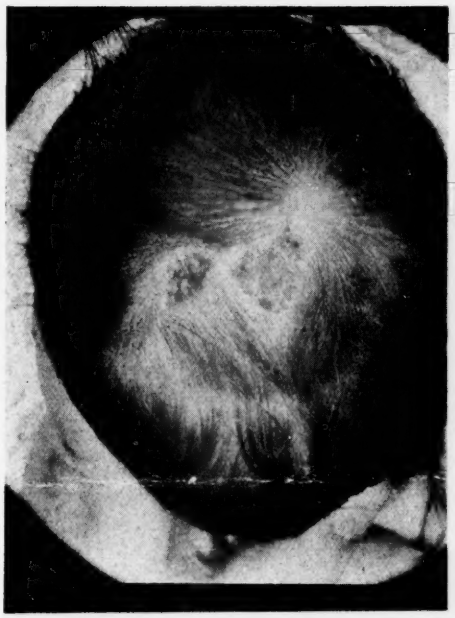

Fig. 1.—Appearance of "congenital" skin defect, two days after delivery.

Case Report

Mrs. E. G., a white private patient, primigravida, aged 25 years, was seen at the twelfth week of pregnancy. The expected date of confinement was Aug. 15, 1944. The past history, family and general history were all negative. The prenatal course was uneventful. On August 17, after a twelve-hour labor, she was delivered of a living, 8-pound male baby. Delivery was facilitated by a left mediolateral episiotomy and outlet forceps. The infant was normal except for the following defect:

At the vertex of the scalp two ulcerated areas were seen, one on each side of the midline. That on the left was 1 cm. by 1 cm. in diameter and that on the right 1.3 cm. by 2 cm. The edges were puckered by beginning cicatrization and the floor appeared raw and irregular with what seemed to be hair follicles situated in the purple-red tissue. No evidence of inflammation was present. Healing progressed rapidly and epithelization was complete on the tenth day post partum. At this time a few fine hairs were seen in the otherwise unbroken layer of glabrous skin.

Treatment consisted of applications of 2½ per cent sulfathiazole ointment for two days; then cod-liver oil ointment until epithelization was complete. No dressings were applied.

The mother immediately accepted the explanation of the defect. The father was suspicious and inferred that the lesion was caused by some negligence on the part of the nursing staff or by an "instrument injury" produced by the obstetrician. Only when the scalp healed was the father at last placated. There was no litigation.

Summary

A case of "congenital" skin defect of the scalp of a newborn infant is reported. A brief résumé of the literature is presented, the accepted explanation of the lesion is discussed and a more specific nomenclature suggested. The importance of these lesions lies in the fact that, through being mistaken for traumatic obstetric injuries, they may be the grounds for litigation.

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MEDICAL BUILDING.

Necrology

HIRAM NAHUM VINEBERG, M.D., a pioneer gynecologist of New York City, died at his home there, May 4, 1945, at the age of 88 years. Born in Russia, Dec. 20, 1857, he came to Cornwall, Ontario, Canada, at the age of five. At 18 he entered McGill Medical School and graduated in 1878 with its highest honor, the Holmes Gold Medal. After a sojourn in London, he went as ship's surgeon to New Zealand, practiced his profession there and then in Hawaii, returning to Canada for a period when he became interested in gynecology and subsequently studied in Berlin, Prague, and Vienna before he settled in New York in 1886.

Dr. Vineberg was attending gynecologist at the Mt. Sinai Hospital in New York and served there from 1893 until his retirement in 1921, after which he was made a consultant. He was also connected in this capacity with Beth Moses and Montefiore Hospitals. A member of many specialist and other medical societies and a Fellow of the American College of Surgeons, he had been a Vice-President of the American Gynecological Society and President of the New York Obstetrical Society. Dr. Vineberg was the author of many contributions to this JOURNAL and its predecessor, as well as to other medical publications. In 1943 a memorial volume was published in his honor by the Mt. Sinai Hospital.

Department of Reviews and Abstracts

Selected Abstracts

Anatomy, Anomalies, Etc.

Power, R. M. H.: The Exact Anatomy and Development of the Ligaments Attached to the Cervix Uteri, Surg., Gynec. and Obst. **79**: 390, 1944.

This article is the first of a series of three dealing with the ligaments and fascia attached to the cervix, and concerns itself with the anatomy of Mackenrodt's ligament. The other two articles, to appear at some future date, relate to the embryology and development of the pelvic fascia and to its clinical significance. A brief review of Mackenrodt's life and his original description of the cardinal ligaments is given.

The author derived his material from four cadavers, two in old age, and two in their sexual prime. In addition, numerous fetuses in various stages of development were examined. In summary the cardinal ligament is described as a connective tissue capsule having an inverted U shape. It is attached medially to the anterior and posterior marginal walls of the cervix and laterally to the white line and fascia of the levator ani. On its posterior superior surface lies the uterine vein, while the artery is anterior. Laterally, an obliquely extending fascial reef is present which deflects the uterine artery anteriorly and the ureter laterally. At the extreme lateral aspect of the ligament the artery crosses the ureter at right angles. The anterior and posterior surfaces are described. Of interest is a foramen or gap between the ligament and the fibers from the levator ani. The triangular space between the three surfaces of the ligament is filled with areolar tissue and smooth muscle.

L. M. Hellman.

Olds, J. M., Swanker, W. A., and Josephson, J. E.: Uterine Malforation, South. M. J. **37**: 436, 1944.

Failure of union in the Müllerian ducts leads to various degrees of uterine deformity. A double uterus is very rare, bicornuate and septate uteri relatively common. The case reported is one of complete double uterus. At operation the left uterus was small but connected to the cervix, and from its upper left cornua emerged a relatively normal-looking tube, and near the fimbriated end was an ovary with multiple follicle cysts. On the right a small uterus was seen densely adherent to the posterior peritoneum and connected with a greatly dilated tube filled with old blood. There was no connection between this uterus and the cervix. Pathologically the right uterus and tube showed a small atrophic uterus lined with secretory endometrium, the tube being the site of a hematosalpinx.

William Bickers.

Abortion

Croisier, M.: The Preventive Use of the Sulfonamides in the Treatment of Abortion, Schweiz. med. Wchnschr. **73**: 1465-1470, 1943.

The author firmly believes that there should be no intervention in cases of abortion when fever is present or in cases of induced abortion even if they are not septic. The favorable outcome in the large majority of cases of uncomplicated abortion is

an argument against the use of large doses of the sulfonamides for prophylactic purposes. At the Lausanne Maternity the author has used "sulfa" therapy prophylactically and therapeutically in cases of abortion. In the febrile cases there was a diminution in the number of days of fever as compared with patients who did not receive sulfa drugs. However, no difference was observed in the control and sulfa group who had no complications. The prophylactic use of sulfa drugs not only did not prevent a fatality but in some cases tended to produce a persistence of mild fever for a long time. Therefore the author says that the preventive use of sulfa drugs in cases of abortion is at present without any value.

J. P. GREENHILL.

Weilerstein, Ralph W.: Intrauterine Pastes, J. A. M. A. **125**: 205, 1944.

The author reports his findings reviewing some abortion fatalities and inquiries in connection with the use of soap pastes. The toxic effects are listed in two groups, systemic and local. The systemic effects, such as hemolysis, jaundice, pulmonary embolism, and septicemia, are the most marked. Sterility (tubal occlusion) and hemorrhage are the two most common local reactions. Peritonitis is not an uncommon finding. The author states that he has been informed by physicians who have used this paste that it is ineffective in 50 per cent of the cases. Appropriate steps have been taken to control the use of soap pastes by the institution and successful completion of legal actions directed at the manufacturers of these products under the Federal Food, Drug, and Cosmetic Act.

WILLIAM BERMAN.

Teare, Donald: Air Embolism in Criminal Abortion, Lancet **247**: 242, 1944.

Teare reports a fatality induced by air embolism following an attempt to induce an abortion of a purported three months' pregnancy. A soap and water mixture were introduced into the vagina by means of the enema syringe. The 18-year-old unmarried girl became immediately cyanotic and collapsed. When the police arrived fifteen minutes later, the patient had expired.

Autopsy revealed a uterus enlarged to the size of a five to six months' pregnancy and contained a male fetus weighing 17.5 ounces. The membranes had been stripped off up to an inch above the lower attachment of the placenta. The placental site contained vessels 0.5 cm. in diameter. The upper part of the inferior vena cava, the right side of the heart and pulmonary artery were found to be pink and filled with bubbles. No bubbles were detected on the systemic side of the circulation. The bubbles were iridescent. The author states that the volume of liquid expelled at one squeeze of an ordinary enema syringe is approximately 43 c.c. and into an enclosed space it is delivered at a pressure which easily reaches 28 cm. of mercury or 380 cm. of water. When the ball-valve end of a syringe was dipped into the frothy soapy water, it was found that about 25 c.c. of air passed through the syringe for every squeeze of the bulb.

C. E. FOLSOME.

Gynecologic Operations

Flax, H. J.: The Use of Cotton Sutures in Lower Abdominal Surgery, Bol. Asoc. méd. de Puerto Rico **36**: 170, 1944.

Continuous cotton thread sutures were used successfully by H. J. Flax in the peritoneal and fascial closure of lower abdominal wounds, thus speeding up the time of operative technique to equal that of catgut. Single unit, number 50, cotton thread is recommended; where stronger suture is needed, this thread is doubled or tripled. One case of incisional hernia in a right rectus incision is reported. This was due to faulty technique with poor approximation of the lower end of the anterior rectus layer, rather than to the use of a continuous cotton suture.

The advantages of cotton thread are: low cost, easy availability; remains stable on exposure to heat and moisture and is easily sterilized; a high coefficient of friction allowing the tying of secure knots; and, that it does not irritate the wound,

since it produces no tissue reaction, thus affording greater comfort to the patient. The only disadvantage to the use of cotton is its lower initial tensile strength as compared with catgut, silk or linen; but this is offset by greater retention of tensile strength in the tissues.

J. P. GREENHILL.

Phelan, G. W.: The Use of Carbolic Acid (Phenol) in the Treatment of Bartholinian Abscess, Am. J. Surg. **64**: 28, 1944.

After incising the Bartholian abscess and evacuating the pus, the author advocates packing the cavity with pure phenol for one and one-half minutes. It is then swabbed with alcohol and packed with iodoform gauze. The method has been employed for ten years with gratifying results.

FRANK SPIELMAN.

Decker, A., and Cherry, T. A.: Culdoscopy, Am. J. Surg. **64**: 40, 1944.

"Culdoscopy" is the term applied by the authors to the direct inspection of the intra-abdominal pelvic organs through the cul-de-sac, using a cytoscope-like instrument called the "culdoscope." With the patient in the knee-chest position, the cul-de-sac is punctured by means of a trochar and cannula, the trochar removed and the instrument introduced. To facilitate inspection of the pelvis a cannula attached to a self-retaining screw tip is applied to the cervix so that the uterus may be manipulated when desirable. Indications for the procedure are sterility, "small ovarian disease," unruptured ectopic, endometriosis, etc. Caudal and local anesthesia are recommended to prevent pain.

FRANK SPIELMAN.

Labor, Management, Complications

Valenzuela, Raul Garcia: Induction of Labor, Bol. Soc. chilena de obst. y ginec. **8**: 226, 1943.

The author has used the following method: at 6 A.M., castor oil, 45 Gm., quinine sulfate, 0.6 Gm.; at 8 A.M., soapsuds enema, quinine, 0.3 Gm.; then every half hour, alternately thymophysin 5 units (0.5 c.c.) and quinine 0.3 Gm. until 20 units of thymophysin and 1.20 Gm. of quinine have been taken.

In most cases the indication was prolongation of pregnancy beyond normal limits: in 33 of the 56 cases the prolongation varied from 4 to 14 days, seventeen having a pregnancy of 290 days or more. Five patients who were admitted with weak pains or premature rupture of membranes requested acceleration of labor to shorten their hospitalization. Exceptional indications were two cases of eclampsism (one with prolonged pregnancy), two of ovular infection, one of uterine fibroma, and one with contracted pelvis (both with prolonged pregnancy).

The series included 25 primiparas and 31 multiparas, and the presentation was vertex 54, breech 2. The entire treatment was given in 37 cases, while only the first doses were needed in some. In five it was impossible to produce efficient contractions, and labor occurred in from 7 to 35 days. In six an obstetric intervention was necessary for delivery and a second induction was needed in four. Spontaneous labor as immediate result of the method occurred in 44 cases (78.57 per cent).

J. P. GREENHILL.

Cabrera, H.: Induction of Labor by Watson's Method, Bol. Soc. chilena de obst. y ginec. **8**: 212, 1943.

The author uses the following method which resembles that of Watson.

(1) Castor oil, 30-60 Gm. (2) Quinine, 0.3 or 0.6 Gm. (3) Soapsuds enema. (4) Pituitary extract, 2.5 to 5 units. (5) Quinine, 0.3 Gm. (6) Pituitary extract, same dose as previously. (7) Continuation of quinine and pituitary until four doses of each are given. The interval between the drugs in this schedule varies from half an hour to one hour. If labor starts, treatment is stopped.

The indications of the method are prolonged pregnancy, infection, membranes ruptured some days previously in which infection is feared, missed labor, habitual death of fetus, and fetal gigantism.

The method was used in 64 patients: 19 primiparas and 45 multiparas. Absolute success was obtained in 4 primiparas and 27 multiparas, or 48.5 per cent. Relative success and relative failure occurred in 11 per cent each, and absolute failure in 28.5 per cent.

There were three fetal deaths, 4.6 per cent, not including a fetus of 1,400 Gm. which died subsequently from prematurity. Three women had simple purulent endometritis and one puerperal pyemia; all recovered. One woman died, 1.5 per cent.

J. P. GREENHILL.

Muñoz, Luis: Aburel's Method. Its Value for Induction of Labor, Bol. Soc. chilena de obst. y ginec. **8**: 87, 1943.

The author reports the results obtained in 28 cases: 15 personal, and the others from various hospitals in the city.

The method consists of injection of a saturated solution of sodium chloride (35 per cent) into the ovular cavity by the transabdominal route, the puncture being made in the midline halfway between the umbilicus and the pubis, after preliminary emptying of the bladder. Local anesthesia is unnecessary. Tincture of iodine is applied to the skin and a lumbar puncture trocar or a large needle for intramuscular injections may be used. To make sure of being in the ovular cavity, a few cubic centimeters of amniotic fluid are aspirated; usually the fluid flows spontaneously from the needle.

The effect of the injection is not immediate, the time needed varying from forty-five minutes to twenty-four hours. Labor is of normal duration. The mechanism of action of the method is unknown. It might be similar to that of the sodium ion on the intestine, which according to Ringer's experiments stimulates the smooth muscle fibers. The method offers no danger to mother or fetus and causes no complications. However, the heart beats of the fetus must be watched.

The method has been used in cases of chronic nephropathy aggravated by pregnancy, of pre-eclampsia and eclampsia, and of prolonged pregnancy. In 12 cases the induction method of Watson had failed even when repeated three times.

The fetuses were alive in 16 of the 28 cases when the method was applied, and 3 died, but the deaths could not be attributed to the method. One patient was operated upon, and four had a labor of over twenty hours. Five had retention of the placenta; one had hemorrhage and manual extraction. Twenty-two had a normal puerperium, five a complication of simple endometritis, and one died of scarlet fever.

J. P. GREENHILL.

Costa, Nicanor Palacios: Partial Symphysiotomy, Bol. Soc. chilena de obst. y ginec. **8**: 94, 1943.

The author states that the method is based on total section of the symphysis fibrocartilage and partial section of the arcuate ligament, the remainder of the latter being separated by forced abduction of the thighs which are maintained in that position. One of the major advantages of this technique is limitation of the use of the knife, thus avoiding possible injury to the urethra, bladder, and cavernous bodies. When the pubic extremities open, the sacroiliac joints act as hinges, their bony surfaces separating, thanks to the softening of the anterior sacroiliac ligaments which are distended. It has been experimentally proved that the separation of the pubic ends after section of the symphysis is 3 to 4 cm., but it may be increased to 5 cm. without rupture of the sacroiliac ligaments. Clinically, the separation needed does not exceed 4 cm.

The correct indication for symphysiotomy implies spontaneous birth. Zarate has given as absolute indication for his operation relative bony dystocia with a conjugate above 7.5 cm. in flat pelves and of 8 cm. in the generally contracted pelves in multiparas with cephalic presentation, ruptured membranes, and complete dilatation or dilatable cervix. He has given as relative indications primiparity, anom-

alies of uterine contraction, incomplete dilatation of the cervix, dystocia of the soft parts, fetal suffering, and slight amniotic infection. He has given as contraindications any bony dystocia with a conjugate of less than 7.5 cm. in flat pelves and 8 cm. in generally contracted pelves, infected primiparas, or those with grave fetal suffering, and dystocia of contraction or of the soft parts.

The statistics of Hospital Rawson show that dystocia was treated with symphysiotomy in 115 cases with two deaths, or 1.73 per cent, and with cesarean section in 93 cases with 15 deaths, or 16.12 per cent.

J. P. GREENHILL.

O'Connell, John E. A.: Maternal Obstetrical Paralysis, Surg., Gynec. and Obst. **79**: 374, 1944.

Five interesting cases of protrusion of the lumbosacral disk associated with pregnancy and labor are described. In each instance paralysis or weakness of the lower extremity was present and all were markedly improved by operation. The author feels that this syndrome with resultant sciatic or femoral pain and/or paresis is a more common complication of pregnancy than generally suspected. It is suggested that hormonal relaxation of the lumbosacral joint may be responsible for the liableness of the disk to rupture.

L. M. HELLMAN.

Ealing, Mildred I.: Amyoplasia Congenita Causing Malpresentation of the Fetus, J. Obst. & Gynaec. Brit. Emp. **51**: 144, 1944.

The author reports a case of amyoplasia congenita in a multipara in which resulted a persistent transverse position of the fetus which was finally rotated to a breech and delivered as such. Amyoplasia congenita is a condition of unknown etiology, characterized by congenital symmetrical joint rigidities of varying degree unassociated with inflammatory change. The condition was associated with hydramnios which is a common concomitant of this fetal abnormality.

WILLIAM BERMAN.

Items

Society of Obstetricians and Gynecologists of Canada

The first annual meeting of this Dominion-wide organization, the Society of Obstetricians and Gynecologists of Canada (La Société des Obstétriciens et Gynécolognes du Canada) was held at Montreal, June 15 and 16, 1945, under the chairmanship of Dr. Léon Gérin-Lajoie, its first president. It has a membership of about ninety Fellows representing all parts of the Dominion and has designated the JOURNAL as its official organ of publication. The complete proceedings of its initial meeting will appear in a subsequent issue.

The officers for the current year are Dr. William A. Scott of Toronto, President, Dr. James Goodwin of Toronto, Secretary.

Correspondence

Complicated Knot of the Cord

To the Editor:

Recently a woman was delivered in this hospital of a 7-pound 3½-ounce male infant with an unusual knot in the umbilical cord. The knot was caught over the posterior shoulder, and difficulty was encountered in delivering the shoulders. The prenatal and postpartum courses were uneventful for both mother and child.

The following pathologic report was given:

"*Gross Description.*—Specimen consists of a placenta which is round and measures 17½ × 16 × 2 cm. The cotyledons are intact. There appears to be a firm band of connective tissue around the periphery of the placenta. The membranes are intact; the cord is slightly eccentric in its attachment being 5 cm. from the nearest edge. The cord appears normal in diameter. However, about 36 cm. from the placenta, a complicated knot is formed in which the cord passes through three loops upon itself. This knot is approximately 8 cm. from the infantile attachment.

"*Microscopic Examination.*—Section through the placenta shows some small foci of early calcification and the usual obliterating vascular changes. No abnormal histologic findings were encountered.

"*Diagnosis.*—Placenta showing an unusual true knot in the umbilical cord."

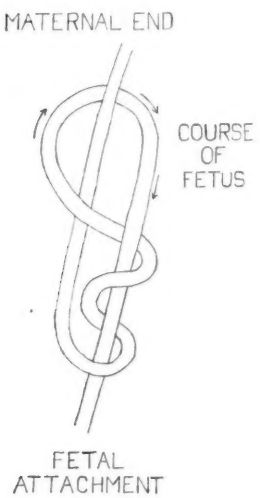

Fig. 1.

According to Ashley[1] the structure was identified as the "Stevedore Knot" (No. 522). However, it is evident from the identification of the fetal (free) and placental (standing) attachments that the knot was formed by the fetus passing through two loops of cord, Fig. 1, instead of merely wrapping the free (fetal) end around the standing (placental) end and passing the free end through the loops as would ordinarily be done.

This case seems to be more complicated than any of the umbilical knots recently described by Hennessy.[2] Moreover, when we trace the course of the fetus in producing this anomaly, it is almost impossible to imagine just how the knot was formed; whereas, if the course had been reversed, the explanation would be relatively simple.

References

1. Ashley, C. W.: The Ashley Book of Knots, Garden City, N. Y., 1944, The Country Life Press, p. 85.
2. Hennessy, J. P.: Am. J. Obst. & Gynec. 48: 528, 1944.

Captain E. C. H. Schmidt, M.C.

Coral Gables, Fla.

Dec. 30, 1944

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Edward A. Schumann, Philadelphia, Pa. *Secretary,* Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting cancelled.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Lewis F. Smead, Toledo, Ohio. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1944.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Dallas, Tex. Annual meeting not announced.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President* Oren Moore, Charlotte, N. C. *Secretary,* T. J. Williams, University, Va. Annual meeting cancelled.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Philip F. Williams, Philadelphia, Pa. *Secretary,* William Mengert, 2211 Oak Lawn Ave., Dallax Tex. Meeting cancelled.

New York Obstetrical Society. (1863) *President,* R. A. Hurd. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Charles A. Behney *Secretary,* John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* James E. Fitzgerald. *Secretary,* Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President* Chas W. Mueller. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. *President,* Edward Friedman. *Secretary,* Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Charles Hunt. *Secretary-Treasurer,* Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* James S. Taylor. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* George Van S. Smith. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Roy J. Hefferman, Brookline, Mass. *Secretary,* Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Goodrich C. Schauffer. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* James R. Costello. *Secretary,* Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* E. L. Zander. *Secretary,* R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. (1924) *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* R. Glenn Craig. *Secretary,* D. G. Morton, California University Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Owen C. Foster. *Secretary,* Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.

Alabama Association of Obstetricians and Gynecologists. *President,* J. M. Weldon, Mobile, Ala. *Secretary,* Eva F. Dodge, Montgomery, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerhard Ahnquist. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* Geo. D. Huff. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* A. L. Carson, Jr. *Secretary,* L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Zeph J. R. Hollenbeck. *Secretary,* Wynne M. Silbernagel, 9 Buttles Ave., Columbus Ohio. Meetings held last Wednesday of each month.

Nassau Obstetrical Society. (1944) *President,* Arthur C. Martin. *Secretary,* William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Jacob Clahr. *Secretary-Treasurer,* J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino Everett. *Secretary,* H. H. Skinner, Yakima. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* J. Milton Singleton. *Secretary,* Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Frank Locke, Winston-Salem. *Secretary,* Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.